BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

EDWARD P. CARTER — ARNOLD R. RICH
WILBURT C. DAVISON — FRANK R. SMITH
GEORGE B. WISLOCKI

VOLUME XXXIX

BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1926

JUL 7 1926

Medical Lib

BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XXXIX, No. 1 JULY, 1926

Contents

The Treatment of Early Syphilis. I. A Plan of Treatment for Routine Use. JOSEPH EARLE MOORE, M.D., AND ALBERT KEIDEL, M.D.. 1

The Treatment of Early Syphilis. II. Clinical Results in 402 Patients. JOSEPH EARLE MOORE, M.D., AND JAROLD E. KEMP, M.D..... 16

The Treatment of Early Syphilis. III. The Wassermann Reaction in Treated Early Syphilis. JOSEPH EARLE MOORE, M.D., AND JAROLD E. KEMP, M.D..... 36

Irradiated Orange Juice. Its Value as an Antirachitic Agent. HERMAN L. MASLOW, DAVID H. SHELLING AND BENJAMIN KRAMER... 56

Book Reviews..... 62

PUBLISHED MONTHLY

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, U. S. A.

Made in United States of America

INFANT DIET MEAD'S MATERIALS

INFANT DIET MATERIALS
for the Hospital

For many years Mead Johnson and Company have been specialists in the manufacture of Infant Diet Materials suitable for the needs of the individual baby.

Let us quote you on the following standard products:

MEAD'S BIOLOGICALLY-ASSAYED COD LIVER OIL

A product correctly handled in our own factory, and tested for its antirachitic potency by our standard method of biological assay.

MEAD'S DEXTRI-MALTOSE

The Carbohydrate of Choice

MEAD'S POWDERED PROTEIN MILK

Prepared from the original Finkelstein formula, and preserved in nitrogen-sealed cans, with a definite dating of expiration on the label.

MEAD'S POWDERED WHOLE MILK

Standardized as to butterfat. May be modified in exactly the same manner as liquid whole milk.

MEAD'S POWDERED LACTIC ACID MILK

Supplied either with Cultured Organisms or acidulated with U. S. P. Lactic Acid.

All of the above products will save the hospital both time and money. *They are always ready for use.*

Special prices will be quoted
to hospitals on request.

MEAD JOHNSON AND COMPANY
EVANSVILLE, INDIANA, U. S. A.

Manufacturers of Infant Diet Materials Exclusively

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.
Copyright, 1926, by The Williams & Wilkins Company

med.
Fac.

THE TREATMENT OF EARLY SYPHILIS

I. A Plan of Treatment for Routine Use[1]

JOSEPH EARLE MOORE, M.D., and ALBERT KEIDEL, M.D.

Baltimore

The purpose of this and the subsequent papers of this series[2] is to describe in detail the results of treatment in a large series of patients with primary and secondary syphilis. The importance of this subject to society, to the individual patient, and to the medical profession cannot be overestimated. From the standpoint of preventive medicine and sociology, the best method of preventing the spread of syphilitic infection is the prompt and adequate treatment of early syphilis. The patient may be spared the disastrous sequelae of late syphilis if his infection is properly managed at the beginning. Paradoxically, the best method of treatment of paresis, tabes, cardiovascular and visceral syphilis is not the treatment of these conditions, but their prevention, by means of thorough early treatment directed against the etiological factor. Finally, the subject is important to physicians because there is as yet no agreement as to standards of treatment, and, as frequently repeated tragedies of inadequately treated syphilis testify, often no real appreciation of the gravity of the problem.

The recent English and American literature on this phase of syphilotherapy, while rich in philosophical and theoretical discussions and in the advocacy of one or another plan of treatment, is singularly vague on actual results. A number of excellent presentations may be found in the German, Austrian, and Scandinavian journals of the past five years. These deal almost exclusively with the results of treatment in early syphilis by the so-called abortive method (one dose to two courses of an arsphenamin product, with or without mercury); but so far as we are aware, none of the European investigators has made use of routine

[1] From The Medical Clinic of The Johns Hopkins Hospital.

[2] Moore, J. E., and Kemp, J. E: The Treatment of Early Syphilis. II. Clinical Results in 402 Patients. III. The Wassermann Reaction in Treated Early Syphilis, *J. H. Hosp. Bull.*, xxxix, No. 1, pp. 10, 36.

E.M. 12.13.20

spinal fluid examinations in evaluating his results. Our own data, based on a quite different treatment scheme, and on the routine employment of lumbar puncture as an indispensable part of the study of every patient, will be compared with certain of the European results, though a detailed survey of the literature will not be attempted.

PLAN OF TREATMENT VERSUS INDIVIDUALIZATION

It is essential to discuss briefly the considerations attending the adoption of a more or less rigid outline of treatment for early syphilis, and to describe the plan in use in our clinic, its evolution, and the reasons for the existence of its important features. We realize that even at the very beginning of a syphilitic infection each patient presents an individual problem in treatment. Were it possible accurately to estimate the virulence of the infecting organism, the ability of the patient to develop resistance against infection, and the probable ultimate influence of such extraneous factors as co-existing or intercurrent diseases or pregnancy, extreme individualization of treatment would be essential. Unfortunately, the influence of these factors on the development of the disease process, so often apparent late in the course of syphilis, can only be surmised when the patient first appears with a chancre or the secondary outbreak.

A group of patients with primary or secondary syphilis differs in three important particulars from any group chosen later in the course of the disease. For the most part, the early syphilitics are healthy young adults, free from extensive anatomic involvement of important viscera, and from the degenerative and sclerotic diseases of advancing years. At this stage of the infection, there is striking uniformity in the character of the lesions and in the distribution of treponemes in the tissues as compared with the varied localizations and lesions of tertiary syphilis. Finally, both clinical and experimental evidence indicate that radical cure, in the sense of eradication of the last treponeme and resultant susceptibility to reinfection, is attainable in early syphilis, but questionable after the disease has existed a year or more, and the organisms have become firmly entrenched in the tissues.[3]

[3] Recent experimental work by Chesney and Kemp from this Clinic, (Chesney, A. M., and Kemp, J. E.: *Jour. Exp. Med.*, 1925, (July), xlii, 17) suggests that the insusceptibility of treated late syphilis to reinoculation may be an expression of

In primary and secondary syphilis, therefore, to attempt individual management of each patient seems less important than to consider him as a member of a more or less uniform group.

Even a brief acquaintance with the literature on reinfection provides evidence that cure of early syphilis may be accomplished by any one of a dozen different treatment plans, or, indeed, by haphazard treatment without definite plan. The problem is to develop a method of treatment which, applied to the whole group, is best calculated to cure the average patient. The justification for the presentation of any scheme of treatment lies in the ultimate results. We do not insist on adherence to the minutiae of our plan, or advocate it as the best method available. Progress toward the evolution of a standard method may be accomplished by a comparison of these results with those of other investigators, working with entirely different treatment plans. Indeed, important modifications of our original system have been suggested by a comparative study of our results and those obtained in Europe from the abortive method.[4]

EARLY DIAGNOSIS AND THOROUGH STUDY OF PATIENT

The first requisites of our treatment plan are early diagnosis and thorough study of the patient. The earlier the diagnosis can be established and treatment started, the better is the chance for radical cure. It is no exaggeration to say that delay of a few days in beginning treatment of primary syphilis may determine unfavorably the ultimate outcome. In addition to clinical and laboratory studies from the standpoint of syphilis, accurate notes of important general anamnestic data, and of the physical and neurologic status are recorded at the first visit. Such an examination frequently reveals unsuspected lesions of syphilis, or co-existing diseases such as tuberculosis, rheumatic heart disease, or nephritis, which may play an important rôle in the patient's reaction to syphilitic infection or in his response

actual immunity remaining after biologic cure, rather than the persistence of living treponemes in the tissues. Though this conception makes the treatment of late syphilis seem more hopeful, it does not alter the view that a second infection of syphilis occurring in a patient previously treated for the disease indicates cure of the first infection.

[4] Moore, J. E., and Kemp, J. E.: *Loc. cit.*

to treatment. From the standpoint of the accurate study of syphilis, this thorough preliminary study provides data for comparison with subsequent examinations. If a patient is regular in his attendance at the clinic, he is submitted to complete physical re-examination every year or two; and he is urged to continue these periodic surveys throughout his life. If he lapses from observation for more than 6 months at any time during treatment, examination is repeated as a routine on his return. The interpretation of abnormalities discovered at these subsequent examinations would be impossible if definite statements regarding pupils, reflexes, glands, cardiac measurements, blood pressure, etc., were lacking from the record of the first visit.

CHOICE OF DRUGS

When the Department of Syphilis was opened in 1914, the essential features of the plan of treatment still in use were formulated by one of us (A. K.). At this time arsphenamin (salvarsan) was the arsenical product in general use. It has remained the drug of choice in our hands for the treatment of early syphilis during the subsequent eleven years. In our opinion, other more recent arsphenamin products, such as neoarsphenamin, sulpharsphenamin, and silver arsphenamin, while valuable under special circumstances and for certain definite indications, cannot compare with arsphenamin in the treatment of early syphilis.[5] Both clinical and experimental evidence indicate that the ease of administration and freedom from reactions of the newer arsphenamin products are more than counterbalanced by loss of therapeutic efficiency. The ultimate place of any drug in syphilotherapy will depend not only on the results obtained in experimental trypanosomiasis or rabbit syphilis, or, from the clinical standpoint, on the rapidity of healing of lesions, or disappearance of treponemes

[5] It is impossible in the brief confines of this paper to enter on a detailed discussion of the relative merits of the various arsphenamin products, and the special indications for the use of each. Our belief in the superiority of the treponemicidal action of arsphenamin is confirmed by the experimental work of Brown and Pearce (personal communication), and by the clinical impressions of such observers as Stokes, Fordyce, and Wile. We deplore equally the tendency to substitute the technically easy administration of neo- and sulpharsphenamin for the slightly more complicated arsphenamin, and the growing exploitation and clinical application of substitutes for arsphenamin without adequate animal experimentation.

from open lesions, or of the reversal of the blood Wassermann reaction; but—a far more important criterion—on the fate of patients years after the cessation of treatment. Comparative data of this type for the various arsphenamin products are so far not available.

Our early experience with arsphenamin paralleled that of other observers. It rapidly became apparent that one or a few injections of the drug would not cure the majority of patients with primary or secondary syphilis, and that treatment must not only be prolonged over a considerable period of time, but that it must include the use of mercury in some form. The inunction method of administration of mercury seemed best to us, because, if properly used, this method is therapeutically efficient; it is free from the drawbacks of the intravenous injection of soluble or intramuscular injection of insoluble salts; it permits a distinct economic gain to patients, who may be temporarily freed from the necessity of weekly visits to the clinic; and finally, because lack of space and medical personnel made other more intensive methods impractical.[6]

It was further determined to use potassium iodide as a routine in all patients, largely on a theoretical basis rather than on definite evidence as to its value in early syphilis. If this drug is of value in dissolving granulomatous tissue, it should enhance the penetrability of arsphenamin and mercury even in the comparatively slight lesions of early syphilis.

Having reached the decision to employ arsphenamin as the arsenical drug of choice, mercury by inunction and potassium iodide, a number of important points arise for decision. Shall these drugs be used simultaneously, periods of treatment thus alternating with periods of rest, during which the patient takes no treatment at all? Or shall treatment be continuous throughout with no rest periods whatever,

[6] We agree with Stokes that mercury by mouth has no place in the treatment of early syphilis. The intravenous or intramuscular administration of soluble salts demands the sacrifice of too much time and money on the part of the patient to be applicable to the working class; and the intramuscular injection of insoluble salts seems to us too dangerous for general use.

Recent experimental and clinical work with various bismuth salts, indicating that the value of bismuth in syphilotherapy may lie between that of arsphenamin and that of mercury, has led us to substitute this drug for mercury in a series of patients with early syphilis. It is too soon to discuss comparative results.

this system involving the alternate use of arsphenamin and mercury? What shall be the dose of arsphenamin, and at what intervals shall it be given? And perhaps most important of all, how long shall treatment be continued? What shall constitute our criteria of cure?

INTERMITTENT VERSUS CONTINUOUS TREATMENT

The decision between intermittent and continuous treatment is of fundamental importance in early syphilis. If arsphenamin and mercury are used simultaneously, it is obvious that after a certain length of time, treatment must temporarily cease, and the patient be allowed to rest. There is a limit of tolerance for vasculotoxic arsphenamin and nephrotoxic mercury, past which it is unwise to push even such healthy young adults as early syphilitics. Furthermore, experimental and clinical evidence has demonstrated that the treponeme may acquire a tolerance for both arsphenamin and mercury, so that after prolonged use of either drug, a dose originally markedly treponemicidal no longer has any effect.[7]

This tolerance is specific for the individual drug employed and is promptly lost when contact between drug and organism ceases. If this phenomenon is universally applicable, it is also obvious that combined arsphenamin and mercury treatment must be temporarily interrupted in order to allow the organisms to lose their tolerance for the two drugs.

A few patients with primary or secondary syphilis may be cured by a single course of arsphenamin alone, or of arsphenamin plus mercury. In the majority, however, biologic cure does not result from a single course of treatment and virulent treponemes remain in various foci in the body. It is of paramount importance to consider the reaction of the patient to these undestroyed organisms. Though the nature of immunity in syphilis is imperfectly understood, the course of events in an untreated infection, with gradually developing insusceptibility to reinfection, and culminating in spontaneous disappearance of the secondary outbreak, the destruction of large numbers of treponemes, and latency, indicates a considerable degree of resistance

[7] The experiments of Akatsu and Noguchi, demonstrating the acquisition of drug fastness *in vitro* (*J. Exp. Med.*, 1917, xxv, 349) have recently been confirmed by Klauder in experimental rabbit syphilis (*Arch. Derm. and Syph.*, 1924, ix, 446).

on the part of the patient. If treatment is begun in the primary or secondary stage of the disease, and the sequence of general tissue reaction, appearance of lesions and their spontaneous resolution is sharply interrupted, the development of the patient's own resistance against the treponeme is wholly or partially prevented. The patient thus enters on the first rest period without adequate resistance against the living treponemes remaining in his tissues, and must elaborate his immune reactions afresh. Depending on the location of the surviving organisms, and the length of time between treatment courses, he may repeat the process of general dissemination and tissue reaction, culminating in delayed or recurrent secondary syphilis; or he may develop that bugbear of early syphilis, a neurorecurrence.

If, on the other hand, treatment is continuous, courses of arsphenamin alternating with courses of mercury, the situation is theoretically quite different. In our opinion, a first course of arsphenamin alone accomplishes as much in the rapidity of healing of lesions, disappearance of organisms, and effect on the blood Wassermann, as does the same amount of arsphenamin plus mercury; at least we are aware of no satisfactory concrete evidence of the advantages of combined treatment in these respects. When the first arsphenamin course has been completed, and the remaining organisms, if present, have perhaps acquired some degree of arsenic tolerance, it is possible to shift at once to mercury. Though the exact method of action of mercury in syphilis is unknown, the consensus of opinion is that, in addition to its comparatively weak parasiticidal effect, it exercises some influence on the patient's own immune processes and may be classed as a "resistance builder." If this conception be accurate, a course of mercury immediately following the arsphenamin course should suffice at least to prevent local growth and redissemination of any remaining foci or organisms, and possibly to destroy some of them by its direct treponemicidal action; while at the same time it may aid the patient to develop his resistance against them.[8]

[8] If the inunction method of administering mercury is employed, the mercury courses must completely fill any time gaps between arsphenamin courses in order to secure continuous drug effect. If mercury must be used simultaneously with arsphenamin, approximately the same continuous effect may be realized if depots of slowly absorbed mercury are established in the body by means of intramuscular

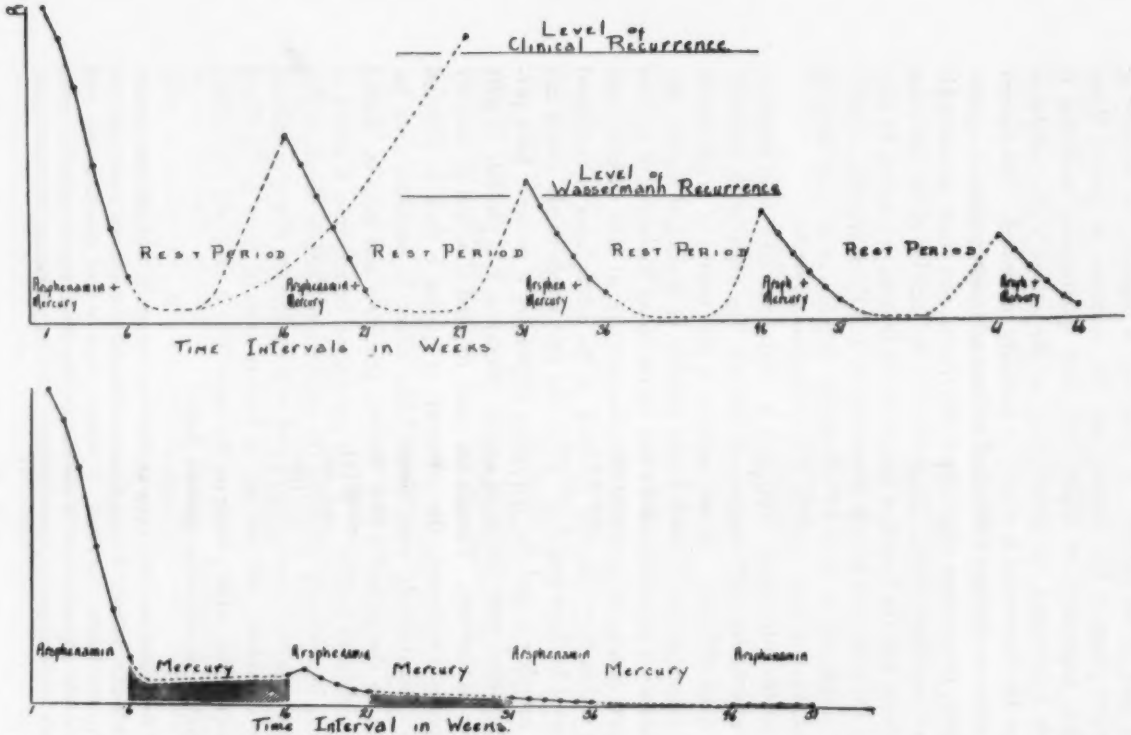

FIG. I. TO SHOW THEORY OF BIOLOGIC RESPONSE TO TREATMENT UNDER (*a*) INTERMITTENT TREATMENT; (*b*) CONTINUOUS TREATMENT

The ordinate represents the number of treponemes in the patient's tissues; the abscissa, the element of time.

After a few weeks of mercury therapy, it may be safely assumed that any arsphenamin tolerance acquired by the organisms in the first course has been lost, and the powerful treponemicidal attack of arsphenamin may again be utilized. This type of continuous treatment with alternating courses of the two drugs may be continued indefinitely without detriment to the patient.

From the purely theoretical standpoint, the course of events under the intermittent and continuous plans of treatment may be shown diagrammatically, as in Figure I. In this chart, the ordinate represents the number of treponemes in the patient's body, the abscissae the element of time. Under the system of combined arsphenamin and mercury courses, separated by rest periods, the chart becomes a series of gradually descending curves, which one hopes may ultimately reach the base line. With continuous treatment with alternating courses of the two drugs, the progress of the curve toward the base line of no organisms and cure is steady and uninterrupted. In the subsequent paper of this series dealing with the course of the blood Wassermann reaction in treated early syphilis, confirmation of these hypothetical curves will be provided.

The dosage of arsphenamin to be employed was adjusted more or less on the basis of expediency. It was felt that in an ambulatory clinic, the danger of reactions from doses as large as 0.6 gm. was sufficiently great to preclude their use. Accordingly, an average dose level of 0.4 gm. for adult men and 0.3 gm. for adult women was adopted.[9] An interval of one week between injections was chosen, not only because of its convenience to the patient, but also to allow time for a maximal effect in resolution of lesions from a single dose, so that maximal tissue penetrability might be secured from subse-

injection of an insoluble salt—provided the rest interval between courses of treatment is not more than 4–6 weeks. We believe, however, that this latter method is too dangerous for general use.

[9] As will be pointed out in the subsequent paper, a comparison of our own actual clinical results from this arsphenamin dosage with those of European workers, who used the abortive system of treatment and a larger dose of arsphenamin, makes it seem advisable to raise the dosage level of the first three injections of the first series to the Ehrlich maximum of 10 mgm. per kilo of body-weight (or approximately 0.1 gm. for each 25 lbs. of body-weight). This modification has accordingly been recently adopted.

quent injections.[10] Eight injections are given in the first series, in order to obtain a maximum of parasiticidal effect early in treatment, while subsequent courses consist of six injections each.

The length of the interim mercury courses early in our experience averaged about three months, but this has gradually been modified in early syphilis in the direction of more arsphenamin and less mercury, especially in the first few months of treatment. This modification is based on the idea of utilizing to the utmost the treponemicidal effect of arsphenamin. At present, the first mercury course is four weeks, gradually lengthened to six, eight, and ten weeks in respective subsequent courses.

LENGTH OF TREATMENT

When this plan was first adopted, we had no accurate idea as to how long this type of treatment should be continued. The evidence provided by patients who lapsed after varying amounts of treatment made it obvious that while a few were cured by one or two courses, many were not cured. Inasmuch as there is no way of differentiating the potential cure from the potential failure before treatment is begun, it seemed certain that the only safe procedure was to treat every patient up to the point necessary to cure the most resistant member of the group. As long as nine years ago, therefore, we set as a standard *one year's continuous treatment after the blood Wassermann (and spinal fluid) had become and had remained completely negative.* The data to be presented regarding treatment results will show to what extent this decision is justified.

CRITERIA OF CURE

The only definite evidence of cure of syphilis in man is reinfection.[11] Tissue transfer, probably the best criterion in the experimental ani-

[10] The chief theoretical objection to the so-called Pollitzer system of massive treponemicidal attack (maximal doses of arsphenamin on each of three successive days) is that no time is allowed for lesions to resolve, and that the treponemicidal effect of the second and third injections is minimized by failure to utilize the factor of tissue penetrability.

[11] The superinoculation experiments of Brown and Pearce (*J. Exp. Med.*, 1921, xxxiii, 553) were carried out only 5 days after a known subcurative dose of arsphenamin, possibly during a negative phase of the animal's immunity. They do not invalidate the conception of reinfection as a standard of cure under all ordinary circumstances.

mal,[12] has not yet been shown to be applicable to man.[13] Necropsy evidence is difficult to secure, and is not altogether certain when obtained, since, to paraphrase Krause,[14] "a systematic and complete search for *Treponema pallidum* in the human body . . . . would involve the serial sectioning of every structure, or the inoculation into animals of each *in toto*, or both."

Lacking more definite standards of cure, we are forced to fall back upon prolonged clinical observation. As applied to our own clinical material, this involves a full year of probation, during which the patient receives no treatment, develops no lesions of syphilis, and the blood Wassermann tested at frequent intervals remains permanently negative. At the end of the year, a complete physical and neurologic examination must show no evidence of progress in the disease, especially in the nervous system or cardiovascular apparatus. The absence of neuraxial involvement must be demonstrated, not only by freedom from neurologic signs, but also by a negative examination of the cerebrospinal fluid. A negative fluoroscopic and roentgenologic examination of the cardiovascular stripe must confirm the negative physical findings in this domain. We have not insisted on the use of the luetin test or the provocative Wassermann procedure because of the uncertain results obtained by ourselves and others.

When a patient has completed the requisite amount of treatment, and has fulfilled these fairly rigid criteria during his probationary period, he is regarded as probably cured, and, if he desires, is allowed to marry. It is nevertheless explained to him that while cure is probable, it is not certain, and that the price of continued good health is eternal vigilance. He is urged to keep himself under observation indefinitely, and to return for periodic physical and serologic examinations for the balance of his life. No patient is ever finally told that he

[12] For complete discussion of the comparative value of experimental evidence of cure, see Chesney, A. M., and J. E. Kemp (*J. Exp. Med.*, 1925 (July), xlii, 33).

[13] Engman and Eberson (*Arch. Derm. and Syph.*, 1921, iii, 347) succeeded in obtaining only 3 positive lymph-node inoculations in 14 attempts from patients with latent syphilis (untreated or not recently treated). Evidently, in man, the lymphoid apparatus is not so constantly a reservoir for the treponeme as in the rabbit.

[14] Krause, A. K.: The Spread of Tuberculous Infection in the Body, *Am. Rev. Tuber.*, 1924, ix, 83.

TABLE I

Plan of treatment for uncomplicated primary and early secondary syphilis

1. *Early diagnosis* and *immediate treatment.* To establish diagnosis, laboratory procedures as necessary (dark field examination, gland puncture, local Wassermann reaction, blood Wassermann reaction).
2. Complete physical and neurologic examination, accurately recorded, before treatment is begun.
3. Treatment:

WEEK	ARSPHENAMIN	MERCURY	BLOOD WaR	REMARKS
	gm.			
1	0.4		1	Recently dosage for first 3 injections has been raised to level of 0.1 gm. for
2	0.4		1	each 25 lbs. of body weight, subsequent injections at dosage of 0.4 gm. for
3	0.4		1	men, 0.3 gm. for women. See discussion in following paper.
4	0.4		1	In average patient all lesions heal rapidly and blood Wassermann becomes
5	0.4		1	negative during first arsphenamin course.
6	0.4		1	
7	0.4		1	
8	0.4	Ung. Hg and KI	1	Mercury overlaps one week at end of first and beginning of second arsphen-
9–12		Ung. Hg and KI		amin course. At this point, a few days without treatment may be danger-
13	0.4	Ung. Hg and KI	1	ous. Neurorecurrence!
14	0.4		1	Arsphenamin starts, mercury stops. Watch for provocative Wassermann
15	0.4		1	after first dose of arsphenamin.
16	0.4		1	Try to prevent even short lapses in treatment, especially at this early stage.
17	0.4		1	
18	0.4		1	
19–24		Ung. Hg and KI		Bismuth intramuscularly may be substituted for mercury, especially if patient
				is uncoöperative with rubs.
				Examine cerebrospinal fluid routinely at about this point.
25	0.4		1	

26	0.4		1	Do not substitute neoarsphenamin unless absolutely necessary. If this is
27	0.4		1	done, dose of neo ought to be maximum (0.9 gm.), and number of injections
28	0.4		1	in a series 8 to 10 instead of 6.
29	0.4		1	
30	0.4		1	
31–38		Ung. Hg and KI		
39	0.4		1	
40	0.4		1	
41	0.4		1	
42	0.4		1	
43	0.4		1	
44	0.4		1	Patients with seronegative primary syphilis may cease treatment here, if blood Wassermann has always been negative.
45–54		Ung. Hg and KI		Note that courses of mercury are gradually getting longer,—4, 6, 8, and now 10 weeks.
55	0.4		1	
56	0.4		1	
57	0.4		1	The average seropositive primary or early secondary patient should have at
58	0.4		1	least 5 courses of arsphenamin.
59	0.4		1	
60	0.4		1	
61–70		Ung. Hg and KI		It is wise to finish treatment with mercury, rather than with arsphenamin.
71–123	Probation.			
	No treatment.		12	Blood Wassermann tested once a month.
124	Complete physical and neurologic examination, spinal puncture, fluoroscopic examination of cardiovascular stripe. Thereafter, yearly physical examination, blood Wassermann every 6 to 12 months. If two spinal fluid examinations have been negative, this need not be repeated.			

is cured and need not return to the clinic. It is only by follow up of this type, carried on for an indefinite period of years, that ultimate success or failure can be recognized.

SEROLOGIC CONTROL OF TREATMENT

This treatment system demands frequent repetition of the blood Wassermann reaction and routine use of spinal puncture. During arsphenamin courses, the blood Wassermann is tested at the time of each injection, or once a week; and the test is carried out at intervals during the interim mercury courses and the probationary period. Routine study of the spinal fluid is carried out in every patient, preferably during the second course of mercury (about 5 months after starting treatment). If spinal puncture is performed earlier than this, some abnormal fluids will be overlooked, because insufficient time has elapsed for the appearance of cyto-biologic changes in the fluid. If carried out much later, certain minor abnormalities will have been cleared up by treatment.[15] Should the spinal fluid prove to be negative at this examination, no change is made in the routine of treatment. If abnormalities are present, treatment is modified in various ways to be discussed in a later communication.

It must be thoroughly understood that the plan outlined applies only to the average uncomplicated case of primary or secondary syphilis. The individual problems presented by those patients who suffer from such complicating diseases as tuberculosis, nephritis, organic heart disease, etc., who develop serious arsphenamin reactions of the dermatitis or jaundice groups, or whose early spinal fluid examination discloses asymptomatic neurosyphilis, cannot be discussed in the space at our disposal. In any event, these problems belong to the legitimate domain of the expert.

For the sake of convenience, a tabular presentation of our treatment scheme is appended. The results obtained from its use will be discussed in the following papers.

[15] For a discussion of this point, see Moore, J. E.: Studies in Asymptomatic Neurosyphilis. II. The Classification, Prognosis, and Treatment of Early Asymptomatic Neurosyphilis, *J. H. Hosp. Bull.*, 1922, xxxiii, 231.

SUMMARY

1. We present a plan of treatment for early syphilis, the essential features of which are

a. That treatment shall be continuous, consisting of courses of arsphenamin alternating with courses of mercury by inunction (or of insoluble bismuth salts intramuscularly) plus potassium iodide.

b. that treatment shall be carried out under detailed serologic control;

c. that treatment shall be prolonged without intermission for one year after the blood and spinal fluid have become and have remained completely negative.

2. Certain reasons attending the adoption of these standards are discussed.

THE TREATMENT OF EARLY SYPHILIS

II. Clinical Results in 402 Patients[1]

JOSEPH EARLE MOORE, M.D., and JAROLD E. KEMP, M.D.

Baltimore

In the nine-year period prior to January 1, 1924, approximately 2500 patients with primary or secondary syphilis have been treated in the Syphilis Clinic of The Johns Hopkins Hospital. Only the exceptionally coöperative patient had completed the full amount of treatment outlined in the preceding paper; and a survey of the material showed that the majority of the group had disappeared from observation. By intensive social service effort, quite a number of delinquents were persuaded to return for careful study, and these, together with the adequately followed patients already available, provide 402 cases of early syphilis for analysis as to the clinical results of treatment.

This considerable group of patients includes those who received varying amounts of treatment, ranging from a single injection of arsphenamin to the completion of our ideal plan. Included also are coöperative patients who faithfully kept every appointment and carried out regular continuous treatment; and an equally large group who, for various reasons, lapsed on one or numerous occasions, and whose progress therefore consisted of courses of treatment alternating with periods of rest. It seemed to us that study of this material might be of value with regard to two of the questions raised in the preceding paper: namely, (1) In early syphilis should treatment be continuous or intermittent? and (2) How long must it be continued in order to attain the maximal probability of cure? In the present paper, the latter of these two points is considered in detail, while the former is dealt with in the third paper of this series.

[1] From the Medical Clinic of The Johns Hopkins Hospital.

CLASSIFICATION OF MATERIAL

Before entering on an actual presentation of figures, it is essential to describe the method of classification of cases, and accurately to define certain of the terms employed. The study is limited to patients with early syphilis,[2] and the material includes 42 patients with seronegative primary, 61 with seropositive primary, and 299 with early secondary syphilis. The seronegative primary group includes those patients whose blood Wassermann reaction at the time of the first treatment was completely negative, and in whom the average duration of the chancre was 14 days. In the seropositive primary group, the duration of the initial lesion ranged from 10 days to 7 weeks (average 3 weeks), and the blood Wassermann reaction on admission was usually completely, but sometimes only partially, positive. All patients classed in the group of early secondary syphilis showed unmistakable cutaneous or mucous membrane lesions at the time of admission, and the average duration of the infection was 3.2 months. No patient is included in this study who had received treatment elsewhere than at our hands.

DEFINITION OF RECURRENCE AND CURE

From the standpoint of the ultimate results of treatment, it seemed simple enough to divide our material into two main groups:—those who were obviously not cured, because they developed clinical or serologic recurrences, and those who, because of the absence of recurrences, might be considered as probably cured. In spite of numerous difficulties in the way of statistical accuracy, this is the general system of classification adopted. For example, a patient who lapses from observation after more or less treatment to return with recurrent secondary syphilis, or a recurrent positive blood Wassermann reac-

[2] This limitation is made in order to provide a rough clinical parallel to the animal experiments of Kolle (*Deutsche Med. Wchnschr.*, 1924, l, 1235), and of Chesney and Kemp (*Jour. Exp. Med.*, 1925, xlii, 17). These workers find that when treatment of syphilitic rabbits is begun before the 45th day of the infection, cure (in the sense of susceptibility to re-inoculation) is uniformly attainable. Later than this, especially after true latency has developed, reinfection is no longer possible. It is hoped later to review our clinical results in late syphilis, in order to carry the parallel further.

tion, is dropped from consideration so far as cure is concerned and is classified only with the recurrences, even though subsequently he may have been adequately treated and fulfilled the rigid requirements for probable cure. This method of classification, applied to all types of clinical or serologic recurrences, obviously reduces the percentage of cured patients.

Likewise, the mere absence of recurrences could not of itself admit the patient to the cure group. Several hundred instances of probable cure were discarded because of inadequate study. In order to qualify as probably cured, a patient must have had no clinical recurrences during treatment, and a full year must have elapsed following the last treatment. Thorough examination at the end of this time must show no physical evidence of syphilis, the blood Wassermann reaction must have been repeatedly negative, and in every instance a negative spinal fluid examination must be obtained. In the majority, also, fluoroscopic and roentgenologic examinations of the cardiovascular stripe, and in a few the provocative arsphenamin procedure, were carried out.

The only exceptions permitted to these rules were the definite examples of reinfection. In our series, no patient is regarded as reinfected unless (1) the first infection was observed in the primary or secondary stage and treated by ourselves. Histories given by patients of infections treated elsewhere, no matter how circumstantial, have been disregarded; (2) in the second infection, the initial lesion, at a different site from that of the first, must be dark field positive, the patient subsequently developing a positive blood Wassermann or secondary syphilis. A number of patients, failing to fulfill these requirements, have been classified under recurrences, though the presumptive evidence for reinfection is strong.

We have divided the recurrent lesions observed into five groups, which are largely self-explanatory. These are (1) recurrent cutaneous or mucous membrane secondary syphilis; (2) neurorecurrences (precocious clinical neurosyphilis predominantly meningeal in type, with or without cranial nerve palsies, appearing suddenly a few weeks or months after inadequate treatment of early syphilis); (3) late syphilis of all types, including tertiary skin, mucous membrane, or bone lesions, visceral and ocular lesions, and cardiovascular syphilis;

(4) neurosyphilis, including paresis, tabes, and late diffuse cerebrospinal syphilis; and (5) Wassermann positive latent syphilis, limited to patients with recurrent positive blood Wassermann reactions, but with no physical evidence of the disease, and in most instances with negative spinal fluid examinations.

It is recognized that many patients with recurrences have escaped notice because of the tendency of the dispensary class of patients to migrate from one to another hospital. This statistical error is more than counterbalanced by the fact that a number of patients, probably cured of their disease, feel so well that they fail to return to any hospital for observation and study. Furthermore, the rigidity of our system of classification of reinfection and probable cure, involving elimination of patients with recurrences of any type, has also operated to make the percentage estimate of cured patients lower than is actually the case.

It is further realized that some individuals now regarded as cured on the basis of long continued negative physical and laboratory evidence, are not really cured, and may develop various late lesions (especially cardiovascular syphilis) in the years to come. The only way to evaluate the importance of this factor is to keep these patients under observation indefinitely and to report upon their status 10, 20 and 30 years hence. It cannot be too strongly emphasized that no syphilitic patient should ever be completely released from periodic medical surveillance.

PROBABILITY OF CURE AFTER VARYING AMOUNTS OF TREATMENT

It is obvious that individual patients differ widely in their response to treatment. Some are cured by a very little treatment. Some will not respond to the most intensive and prolonged effort. In general, however, the longer treatment is continued, the greater are the chances of cure. In order to obtain some estimate of the percentage probability of cure after varying amounts of treatment, we have divided our material into four treatment groups, as follows:

Group I: patients receiving from 1 to 8 injections of arsphenamin. In most of these, mercury was used either not at all or for less than 1 month.

Group II: patients receiving from 1 to 2 courses of arsphenamin

(6–12 injections), mercury having been used at least 2 months in the interim between arsphenamin courses.

Group III: patients receiving three courses of arsphenamin (13–20 injections) with interim mercury.

Group IV: patients receiving four or more courses of arsphenamin (21–40 injections) with interim mercury. In this group fall all patients who have completed the ideal course of treatment outlined in the preceding paper.

TABLE I

Results of treatment in seronegative primary syphilis

AMOUNT OF TREATMENT, GROUP	TOTAL NUMBER OF PATIENTS	PROBABLE CURES, INCLUDING REINFECTION	REINFECTION	CLINICAL AND SEROLOGIC CURE MAINTAINED FOR							RECURRENCES, ALL TYPES
				1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6–7 years	7–8 years	
I	17	4 (23.5%)	2	1	1						13 (76.5%)
II	11	5 (45.4%)	1	1	1	2					6 (54.6%)
III	7	6 (85.7%)	1	1	3		1				1 (14.3%)
IV	7	7 (100%)	1	5	1						

CLINICAL RESULTS IN EARLY SYPHILIS

In Tables I and II appear the results of treatment in 42 patients with seronegative primary syphilis, and 61 with seropositive chancres. Though the number of cases is small, nevertheless, as expected, the percentage probability of cure mounts rapidly with increasing amounts of treatment. Of 14 seronegative primary patients receiving 13 or more injections of arsphenamin plus mercury, only one has developed a recurrence of any type. The results in the seropositive primary group are notably poorer, emphasizing the extreme importance of early

TABLE II

Results of treatment in seropositive primary syphilis

AMOUNT OF TREATMENT: GROUP	TOTAL NUMBER OF PATIENTS	PROBABLE CURES, INCLUDING REINFECTION	REINFECTION	CLINICAL AND SEROLOGIC CURE MAINTAINED FOR							RECURRENCES, ALL TYPES
				1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6–7 years	7–8 years	
I	31	3 (9.7%)	2					1			28 (90.3%)
II	17	8 (47%)	2	2	2	1				1	9 (53%)
III	6	3 (50%)		2		1					3 (50%)
IV	7	4 (59.1%)	1	2				1			3 (40.9%)

TABLE III

Results of treatment in early secondary syphilis

AMOUNT OF TREATMENT: GROUP	TOTAL NUMBER OF PATIENTS	PROBABLE CURES, INCLUDING REINFECTION	REINFECTION	CLINICAL AND SEROLOGIC CURE MAINTAINED FOR							RECURRENCES, ALL TYPES
				1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6–7 years	7–8 years	
I	148	14 (9.5%)	1		2	5	2		3	1	134 (90.5%)
II	61	20 (32.8%)	5	4	1	2		3	2	3	41 (67.2%)
III	33	17 (51.6%)		4	5	1	4	1	1	1	16 (48.4%)
IV	57	45 (76.2%)	3	15	14	8	3	2			12 (23.8%)

treatment. Only half of those patients receiving 13 or more arsphenamin injections can be regarded as cured. The numbers are of course too few for statistical accuracy.

A similar arrangement of 299 patients with early secondary syphilis is shown in Table III. Here the number is large enough to permit of accurate conclusions. After eight or less doses of arsphenamin, 10 per cent are cured, while 90 per cent develop recurrences. When treatment is prolonged to the amount represented by Group IV, these figures are almost reversed. Reinfection occurs almost as frequently following small amounts of treatment as after large amounts, especially in primary syphilis.

If seronegative and seropositive primary and early secondary syphilis are considered as a single group, one finds that, after Group I treatment, 10.8 per cent of patients are probably cured; 89.2 per cent develop some type of recurrence. Group II treatment results in 37.1 per cent of probable cures, with 62.9 per cent of recurrences; Group III treatment in 56.6 per cent, and Group IV in 78.8 per cent of probable cures, with only 43.4 per cent and 21.2 per cent, respectively, of recurrences. Excluding reinfections, half of the probably cured group have been followed for more than 3 years. Of the 15 recurrences after Group IV treatment, no less than 9 might have been interpreted as reinfections under a less rigid system of classification, and, if we had permitted ourselves this laxity, the probability of cure after Group IV treatment would be 91.5 per cent instead of 78.8 per cent. These data demonstrate afresh that some patients (10 per cent) may be cured by a very little treatment (Group I), while some others (20 per cent) are not cured by a great deal (Group IV).

Using a system of treatment analogous to that which we have outlined, the minimal amount of treatment necessary to cure the average early syphilitic after the blood Wassermann reaction has become positive appears to be at least four courses of arsphenamin plus interim mercury. This approaches very closely the requirements originally laid down some nine years ago,—*a full year of treatment after blood and spinal fluid have become, and have remained, completely negative.* The only exception to the rule is in seronegative primary syphilis where three courses of arsphenamin plus interim mercury, extending over about 9 months, are apparently productive of satisfactory results.

COMPARISON OF OUR RESULTS WITH THOSE OBTAINED BY THE ABORTIVE METHOD

An important modification of our treatment plan is suggested by a comparison of these results with those reported in the German and Scandinavian literature from the so-called abortive system of treatment. This plan is subject to various modifications in European Clinics, but in general it consists of a single short intensive course of treatment for seronegative primary syphilis, extended to two or three similar courses for seropositive primary or early secondary syphilis. Arsphenamin is the arsenical drug of choice, with silver arsphenamin less frequently used. An arsphenamin course consists of from 3 to 8 injections, the first few or all of which are of maximal dosage (10 mgm. per kilo, or roughly 0.1 gm. per 25 pounds of body-weight). All plans include the use in some form of simultaneous or interim mercury or bismuth. Although *a priori* one would expect a much greater incidence of serious arsphenamin reactions from repeated doses of this size (0.4–0.7 gm., depending on body-weight) than from the lower average doses which we have employed, the system has been used abroad in a very large number of patients without disastrous results. The dosage level of 10 mgm. per kilo of arsphenamin has repeatedly been demonstrated to be curative in rabbit syphilis; and if the objection of serious reactions may be overcome, it certainly seems advisable to apply it to man.

The limits of this paper prevent extended reference to the European literature, but attention is drawn to noteworthy communications by Rost,[3] Silberstein,[4] Boas,[5] and Müllern-Aspegren.[6] The first, conducting a questionnaire on behalf of the German Dermatological Society, reports on 1602 cases of seronegative, and 1391 of seropositive, primary syphilis, treated by variations of this method in various clinics. Clinical and serologic cure was obtained in 85 per cent of the seronegative

[3] Rost: Abortivbehandlung der Syphilis, *Arch. f. Derm. u. Syph.*, 1922, cxxxviii, 89.

[4] Silberstein, S.: Ueber Abortivheilung der Syphilis durch eine kombinierte Salvarsan-Quecksilberkur. *Ibidem*, 1923, cxliii, 334.

[5] Boas, H.: Die Abortivbehandlung der Syphilis. *Acta Derm.-Vener.*, 1922, iii, 559.

[6] Müllern-Aspegren: Abortivbehandlung der Syphilis. *Acta Derm.-Vener.*, 1922, iii, 572.

primary, and in 68.5 per cent of the seropositive primary cases. The other investigators detail similar and even better results. These data are not strictly comparable with our own, because none of these European workers have employed routine spinal fluid examination as a criterion of cure; some investigators regard one or several negative blood Wassermann reactions as adequate evidence of cure; and their reports are generally limited to patients who have completed the desired course of treatment. For example, Silberstein, after recording 91 per cent cures in primary, and 72 per cent cures in early secondary syphilis from the use of his complete treatment scheme, states that of 100 patients who received too little or too irregular treatment (further details not given) only 50 per cent of primary and 33 per cent of secondary syphilis were cured. Our own material, controlled by routine spinal puncture, is wholly unselected, and attempts to picture results after insufficient as well as after adequate treatment. Some analogy may be drawn between our results and these European reports if we select from our material patients who have completed Groups III and IV treatment (three or more courses of arsphenamin plus interim mercury) as representative of the results of our plan of treatment carried out in whole or in great part. In these two treatment groups, our results show 92.8 per cent probable cures for seronegative primary, 53.8 per cent for seropositive primary and 68.8 per cent for early secondary syphilis. Allowing for the differences in methods of study and for the small number of cases involved, there is striking similarity in the results from the two methods of treatment.

When it is remembered, however, that these European results have been achieved with less treatment, in point of time, than our own, it seems fairly certain that in early syphilis the use of maximum doses of arsphenamin (10 mgm. per kilo of body-weight) early in treatment is productive of better end results than the average lower dosage which we have employed. We have accordingly modified our treatment scheme, as indicated in the tabular summary in the preceding paper, by raising the dose of the first three arsphenamin injections to 10 mgm. per kilo of body-weight, subsequent injections being 0.3–0.4 gm. for the average adult. As our experience so far has indicated, in ambulatory practice there is undoubtedly added risk of serious reactions from the higher dosage, but the apparent gain in therapeutic results may

justify the risk, if it is not too far prolonged. It is because of our fear of delayed reactions of the dermatitis and jaundice groups that we have dropped back to the average rather than the maximal dose after three injections.

The second significant alteration in our treatment plan may also be mentioned at this point. There is now sufficient experimental and clinical evidence to indicate that bismuth, the mode of action of which in syphilis is probably analogous to that of mercury, may be intermediate in value between arsphenamin and mercury. For this reason, we have substituted interim intramuscular injections of a bismuth preparation for the first course or two of mercury inunctions, in the hope of more certain ultimate sterilization of the patient.

Our experience with late recurrences, and the growing European opinion that abortive treatment is applicable only to seronegative primary syphilis, lead us to feel that, even with these alterations in plan, it is inadvisable materially to shorten the total length of treatment, and on this point we still adhere to our original standards. It is far better to overtreat a few patients than to undertreat many. It will, of course, be impossible to estimate the effect of these changes on end-results for at least five years.

DELAY IN DIAGNOSIS AND TREATMENT PRODUCES UNFAVORABLE RESULTS

As many investigators have pointed out, the earlier treatment of a syphilitic infection can be started, the better are the chances of ultimate cure. This is admirably shown by our own material, summed up in Table IV. Here are presented end-results for seronegative and seropositive primary and for early secondary syphilis, *without regard to the amount of treatment or its character*. Especial attention is directed to the incidence of reinfection in the three groups: 11.9, 8.1, and 3.0 per cent, respectively. The difference in time of starting treatment in these three groups of patients is at most a few weeks, and as between the seronegative and seropositive primary patients only a few days, yet there is a significant difference in the probability of cure. Data such as these fully justify every effort for early diagnosis, which, let it be emphasized, must in the majority of instances be made by dark field. It is absolutely inexcusable deliberately to

wait for the appearance of a positive blood Wassermann reaction or of early secondary syphilis. Delay of this kind means reducing the probability of cure about fifty per cent.

It has been stated that better end results might be obtained if the patient's own defense mechanism against syphilitic infection were utilized by deliberately allowing him to develop the generalized tissue reaction of secondary syphilis before instituting treatment. The slightly higher percentage of cures in our series of secondary as compared to seropositive primary syphilis is of interest in this connection. It must not be forgotten that in order to take full advantage of whatever immunity the patient may develop, one must wait, not only for the appearance of secondary syphilis, but for its spontaneous healing and the development of true latency, a process which takes from 3 months to 2 years. There is no adequate evidence that treatment

TABLE IV

To show the superior results of early treatment

	TOTAL CASES	CURES, INCLUDING REINFECTIONS	REINFECTIONS	PER CENT CURED	PER CENT REINFECTED
Seronegative primary	42	22	5	52.3	11.9
Seropositive primary	61	18	5	29.5	8.1
Early secondary	299	96	9	32.1	3.0

begun in the latent period is productive of better or, for that matter, of as good results as when it is begun as soon as the diagnosis can be established. Even if the end-results for the patient himself were vastly better, the public health aspect cannot be ignored. Lacking facilities for complete isolation of all early syphilitics, which could not be enforced even if available, it is out of the question to allow infectious lesions in irresponsible patients to go untreated for any appreciable length of time, much less weeks, months or years. The spread of syphilis under such conditions would be appalling.

ANALYSIS OF RECURRENCES OBSERVED

In Table V is presented an analysis of the types of recurrences observed in our material. Little comment on these figures is neces-

sary. The extremely high incidence of recurrent secondary syphilis and neurorecurrences after Group I and II treatment must be pointed out. Among the 15 patients with recurrences after Group IV treatment, four classed under recurrent secondary syphilis and 5 of those with recurrent positive blood Wassermann might be regarded as showing reinfections (and therefore cures) under a less rigid system of interpretation. If one groups together as serious recurrences those which greatly impair efficiency or endanger life (neurorecurrences, tertiary

TABLE V

Type of recurrences observed in 402 cases of early syphilis

AMOUNT OF TREATMENT. GROUP	TOTAL NUMBER OF PATIENTS IN GROUP	CURES	RECURRENCES. ALL TYPES	RECURRENT SECONDARY SYPHILIS	NEURORECURRENCES	LATE SYPHILIS (TERTIARY, CARDIOVASCULAR)	NEUROSYPHILIS	LATENT (WaR RECURRENCES)	PATIENTS DEVELOPING TWO OR MORE TYPES OF RECURRENCES (EXCLUDING LATENT)
I	196	21 (10.8%)	175 (89.2%)	40	38	35	15	59	12
II	89	33 (37.1%)	56 (62.9%)	9	17	10	6	17	3
III	46	26 (56.6%)	20 (43.4%)	5	4	2	5	5	1
IV	71	56 (78.8%)	15 (21.2%)	4		1	1	9	

syphilis and neurosyphilis), the incidence of these falls from 44 per cent after Group I treatment to 37 per cent after Group II, to 24 per cent after Group III, and to only 3 per cent after Group IV. For all practical purposes, therefore, a satisfactory result (cure or arrest) may be obtained in 90 to 95 per cent of all patients with early syphilis treated for a sufficiently long period of time.

Again, putting aside for the moment the factor of the amount of treatment given, one finds that these three serious types of recurrences

represent, for the group of seronegative primary syphilis, 35 per cent of all the observed recurrences; for the seropositive primary group, 47 per cent; and for early secondary syphilis 53 per cent. This is perhaps the strongest available argument for the early diagnosis and treatment of the disease.

RECURRENT SECONDARY SYPHILIS

The majority of the 55 patients in the group of recurrent secondary syphilis received very little treatment, which was often taken in a haphazard irregular manner. Only 7 patients, or 12 per cent, received as much as 2 courses of arsphenamin with interim mercury, while 41, or 74.6 per cent, took 9 or less doses of arsphenamin with no mercury. The average lapse between treatment and recurrence was 8.1 months, there being comparatively few recurrences in less than 3 months. In 8 instances, definite cutaneous or mucous secondary relapses were observed more than one year after the last treatment. One patient, who had received 4 doses of arsphenamin at very irregular intervals, returned $4\frac{1}{3}$ years after the last injection with bilateral acute iritis. In no less than 12, or 21.8 per cent of the patients in this group, there was more than one outbreak of recurrent secondary syphilis, this tendency to repeated recurrences being especially noteworthy in the case of ocular lesions (iritis, uveitis, neuroretinitis, etc.). Three patients also developed neurorecurrences; and one individual, some years after his recurrent secondary outbreak, was readmitted with a tertiary bone lesion, and again subsequently with paresis. In a number of instances, the recurrence proved to be a salutary lesson to the patient, who subsequently submitted to adequate treatment, although, as we have stated, such patients are not included among our cure group.

NEURORECURRENCES

Fifty-eight patients developed neurorecurrences. As in the case of recurrent secondary syphilis, treatment is featured by its utter inadequacy, the majority of patients (55 per cent) having received 6 or less doses of arsphenamin without mercury before the appearance of the neurorecidive. A striking difference between the two groups is apparent, however, in the length of the lapse after treatment. In

every patient in the neurorecurrence group, the symptoms appeared within the first year, and in 97 per cent within the first 6 months. The average lapse was only 2.7 months, as opposed to 8.1 months in the recurrent secondary group; in 2 instances the interval without treatment was only 1 week, and in 16 patients one month or less. That precocious neurosyphilis can develop under these conditions is one of the strongest arguments for the continuous treatment of early syphilis. After once beginning treatment, it is absolutely unsafe to permit a patient with primary or secondary syphilis to pass a single day without the influence of a treponemicidal drug. The types of neurorecurrence observed include acute syphilitic meningitis, cranial nerve palsies, the 7th and 8th cranial nerves being most frequently involved, precocious vascular neurosyphilis, etc. The treatment of this spectacular complication, a special problem outside the scope of this paper, will be discussed, together with the ultimate fate of such patients, in a later communication.

TERTIARY SYPHILIS

Late recurrences, including neurosyphilis (other than neurorecurrences) occurred in 72 patients. The average interval between treatment and recurrence is here to be measured in years rather than months, that for the various types of tertiary syphilis being 29 months and for neurosyphilis 3 years. The types of tertiary syphilis observed include 18 instances of skin, mucous membrane, or osseous lesions, 4 of visceral and ocular syphilis, 24 of cardiovascular involvement, and 27 of neurosyphilis. The two latter are presently considered in more detail. It has frequently been suggested that tertiary syphilis, and especially neurosyphilis, is more common after inadequate modern treatment than in patients untreated or treated only with mercury. Barring the neurorecurrence type of neuraxis involvement, we do not believe this to be true, though of course insufficient time has elapsed to allow accurate statements. Considering our group of patients as a whole, however, approximately 11 per cent have ultimately developed tertiary syphilis and 6 per cent late neurosyphilis, an incidence certainly well below that of a similar untreated group. Nor is there any evidence that tertiarism or clinical neurosyphilis appears earlier after inadequate modern treatment than in the mercurial era. The

time intervals between treatment and onset of late symptoms in our series of patients are approximately those given by Fournier many years ago. The relative rarity of gummatous tertiarism is illustrated in our series by the small number of patients with skin, bone, mucous membrane, or visceral lesions; and it is worthy of special comment that of the 22 patients who developed lesions of this type, 16, or 72 per cent, had received 8 or less doses of arsphenamin without mercury (Group I treatment). Apparently, therefore, a moderate amount of treatment affords adequate protection against ordinary tertiarism.

CARDIOVASCULAR SYPHILIS

Cardiovascular syphilis, especially aortitis (but including also one instance of aneurysm and two of aortic regurgitation) was the most frequent single type of late lesion observed (24 cases). We have repeatedly been impressed by the extreme difficulty of early recognition of syphilitic aortitis or myocardial disease, these diagnoses having often been made in life when necropsy failed to disclose the lesions; or conversely, the first intimation of their existence being revealed by necropsy. We believe, however, that aortitis is much more frequently overlooked, when present, than diagnosed when absent. In the present series, the diagnosis is based on repeated careful physical examination and in most instances fluoroscopic and roentgenologic examinations, as well as by attention to such symptoms as substernal pain, dyspnea, and cough. It is probable that the actual incidence of cardiovascular syphilis is higher than we have indicated, and that in subsequent years this group of patients will be enlarged at the expense of our cured group. This type of late lesion appears later than ordinary tertiarism, the average lapse between the last treatment and the detection of the cardiovascular lesion being 46 months. Here, as with more obvious tertiary lesions, a little treatment seems to have done much to protect the patient, since all the observed cardiovascular syphilis occurred after Groups I and II treatment, and none at all after a moderately adequate amount.

LATE NEUROSYPHILIS

Included under this heading are 27 patients who developed clinical signs or symptoms of central nervous system syphilis, at an average

interval of 3 years following the last treatment. In 4 instances, the type of neurosyphilis was general paresis, in one a vascular accident and, in 22, diffuse meningovascular involvement. Many of these latter patients had no symptoms pointing to the nervous system, the lesions being detected on the basis of pupillary or reflex abnormalities, confirmed in each instance by positive spinal fluid changes. We have discarded from our material as inadequately studied a number of patients in whom minor neurologic changes were present, but spinal fluid examinations lacking. It is noteworthy that not a single case of tabes dorsalis is represented in our series. This, together with the small number of paretics observed, is explainable by the comparatively short period of time covered by the survey (2–10 years). Eight of the patients now diagnosed as having diffuse cerebrospinal syphilis show the typical paretic spinal fluid formula, and are potential candidates for paresis in later years. It should also be pointed out that, unlike other late recurrences, neurosyphilis occurred in 6 patients who had had Group III or IV treatment, illustrating the difficulty of eradicating completely this disastrous end-result.

We have not included in this group patients found to show spinal fluid abnormalities at the time of the first routine lumbar puncture; indeed, several such instances are represented in the cure group. Especial interest has attached to the reëxamination of those patients in whom early routine spinal fluid findings were negative. Several years ago we expressed the opinion[7] that in the majority of cases of neurosyphilis, invasion of the central nervous system by the treponeme occurred during the first few months of the infection; but that a nervous system which had escaped this early invasion might be involved at a later date, provided a second or later period of general dissemination of organisms and spirochetemia occurred. The outward and obvious evidence of redissemination of organisms consists either of recurrent secondary syphilis or perhaps of a recurrent positive blood Wassermann reaction. In 54 of the patients considered in this paper, an early negative spinal fluid examination was followed by one or more subsequent lumbar punctures, the second or succeeding tests usually being made at least 2 years after

[7] Moore, J. E.: The Genesis of Neurosyphilis. *Arch. Derm. u. Syph.*, 1921, iv, 55.

the first negative result. The subsequent spinal fluid examination was negative in 51, or 94 per cent, and none of these patients have developed clinical neurosyphilis. In 3 instances, or 6 per cent, a negative spinal fluid test was followed by a positive one; but each of these three patients had developed either recurrent secondary syphilis, or a Wassermann recurrence, or both, between the time of the first and second spinal fluid examinations. This would seem to establish as a valid general rule that in early syphilis, if routine examination of the spinal fluid carried out after 6 months' treatment is negative, the patient will not develop clinical neurosyphilis or a subsequently positive spinal fluid unless a second opportunity for nervous system invasion is afforded by subsequent redissemination or organisms, manifested by a clinical or a blood Wassermann recurrence.

BLOOD WASSERMANN RECURRENCES (LATENT SYPHILIS)

In 88 patients there developed recurrent positive blood Wassermann reactions, but no clinical evidence of syphilis. Forty-one patients of this group represent true latent syphilis, since in addition to the negative physical evidence, the spinal fluid reëxamined at the time of the blood Wassermann recurrence was found to be negative. In the remaining 47 instances, spinal fluid examinations were not obtained, so that about a fourth of these patients probably belong in the neurosyphilis group. Here, as with other types of recurrence, treatment is marked by its inadequacy, only 23.8 per cent having received two or more courses of arsphenamin plus interim mercury. In 9 instances a recurrent positive blood Wassermann developed after completion of more than a full year's treatment. As already stated, five of these 9 patients might be regarded as having reinfections with a little relaxation of our rigid standards. The tendency for serologic recurrence to be delayed until long after inadequate treatment is well illustrated by the fact that the average interval between treatment and recurrence is 17.7 months. In the majority of instances, of course, the recurrence might have been detected earlier, had symptoms prompted the patient to return.

MULTIPLE RECURRENCES

As we have pointed out, more than one type of clinical recurrence (excluding a mere recurrent positive blood Wassermann reaction) developed in 16 patients, or 8 per cent of the total number with clinical recurrences. In three instances, a neurorecurrence was simultaneous with, or was followed by, recurrent secondary syphilis. One of these patients subsequently developed late diffuse cerebrospinal syphilis. Four patients, whose first relapse was a neurorecurrence, later developed gummatous tertiary skin or bone lesions, and in three of these the catalogue of recurrences was closed by the final appearance of paresis. In seven instances there were found, simultaneously or in sequence, various types of tertiary lesions and also late neurosyphilis; and in two cardiovascular syphilis was combined with other recurrent lesions. These cases illustrate the value of frequently repeated complete surveys, and the tendency of late syphilis to involve more than one system or organ.

SUMMARY

1. We report the clinical results of treatment in 402 patients with early syphilis, of whom 42 had seronegative primary, 61 seropositive primary, and 299 early secondary syphilis.

2. In this study, a patient is regarded as probably cured if he is reinfected; or, if a complete survey, including physical examination and tests of the blood and spinal fluid, carried out at least one year after the date of the last treatment, shows no evidence of syphilis. About half of our presumably cured patients have been followed for more than 3 years of probation.

A patient with a clinical or serologic recurrence of any type occurring during or subsequent to treatment is classified only with treatment failures.

3. Under a system of continuous treatment with alternating courses of arsphenamin and mercury, the probability of cure is in direct proportion to the duration and regularity of treatment. Only 10 per cent of those patients receiving 8 or less doses of arsphenamin without mercury were cured; when two courses of arsphenamin plus interim mercury were given, 37 per cent were cured; after three courses, 56

per cent, and after four or more courses, 78.8 per cent of probable cures were obtained.

4. The optimal amount of treatment for early syphilis with the plan advocated appears to be a full year of treatment after the serology of blood and spinal fluid have become and have remained negative, excepting only seronegative primary syphilis, in which a three course treatment, lasting 9 months, apparently produces satisfactory results.

5. Grouping together coöperative and uncoöperative patients, without regard to the character or duration of treatment, it is shown that if treatment can be begun within the first two weeks of the infection (seronegative primary syphilis), the chance of ultimate cure is almost twice as great as when it is delayed until the appearance of secondary manifestations. In particular, the incidence of reinfection in the groups of seronegative and seropositive primary and early secondary syphilis is 11.9, 8.1, and 3.0 per cent respectively. The extreme importance of early and accurate diagnosis is thus emphasized.

6. With the utmost coöperation on the part of the patient, and painstaking treatment and follow-up on the part of the physician, it appears possible to cure 100 per cent of patients with seronegative primary syphilis, but only 80 to 95 per cent of those with seropositive primary or early secondary syphilis. The refractory 5 to 20 per cent seem likely, in spite of the utmost efforts of therapy, to develop late syphilis, especially neurosyphilis.

7. A comparative study of the results obtained from our plan and from the abortive system of treatment in vogue in Europe suggests modifications of our treatment system, which we have discussed, although essentially similar results have been obtained from the two methods.

8. The recurrences observed in our material, classified into the groups of recurrent secondary syphilis, neurorecurrences, tertiary syphilis, late central nervous system syphilis, and Wassermann positive latent syphilis, are described and analyzed as to the amount of treatment received and the interval between treatment and clinical or serologic relapse.

9. Recurrences seriously impairing efficiency or endangering life (neurorecurrences, tertiary syphilis, neurosyphilis) occurred in almost half the patients receiving 8 or less injections of arsphenamin; in a third

of those receiving from one to two courses of arsphenamin plus mercury; in a quarter of those receiving three treatment courses; but in only 3 per cent of those patients receiving four or more arsphenamin courses plus mercury. The necessity of long continued treatment is thus emphasized.

10. The tendency of inadequately treated syphilis to repeated relapses in the same patient is pointed out.

11. The short average time interval (2.1 months) between the date of the last treatment and the onset of neurorecurrences emphasizes the necessity of continuous treatment in early syphilis.

12. Cardiovascular syphilis, especially aortitis, was the most common type of tertiary recurrence observed.

13. Twenty-seven patients developed neurosyphilis, usually of the diffuse meningo-vascular type. The relative infrequency of general paresis (4 cases) and of tabes dorsalis (no cases) is explainable on the basis of the short period of years covered by this study.

14. The evidence of repeated routine spinal punctures in 54 patients permits the general statement that in early syphilis, if the spinal fluid is normal after 6 months' treatment, the patient will not develop clinical neurosyphilis or a subsequently positive spinal fluid unless a second dissemination of organisms (clinically manifest by recurrent secondary syphilis or a recurrent positive blood Wassermann) occurs.

15. Periodic reëxaminations from physical and serologic standpoints are absolute essentials in the evaluation of treatment results. Even though prolonged observation makes cure seem almost certain, a syphilitic patient should never be released from the obligation of periodic reëxamination throughout his life time.

THE TREATMENT OF EARLY SYPHILIS

III. The Wassermann Reaction in Treated Early Syphilis[1]

JOSEPH EARLE MOORE, M.D. and JAROLD E. KEMP, M.D.

Baltimore

In the plan for the treatment of early syphilis, outlined in the first paper of this series,[2] the blood Wassermann reaction has been freely used as an index of progress. A Wassermann reaction has been performed at the time of each intravenous injection of arsphenamin, occasionally in the interval between arsphenamin courses, and at frequent intervals after the patient has been placed on probation. During a complete course of treatment with subsequent observation, Wassermann tests have been done on not less than 50 different occasions, most of the time at weekly intervals. This procedure provides data unobtainable by the more prevalent system of performing the test only before and after each course of treatment.

The technic employed has not varied in the 10-year period on which these papers are based,[3] except for the introduction of the icebox modification. In order not to complicate the results, the method of icebox fixation is not considered in this paper.

STATISTICAL METHOD EMPLOYED IN ARRIVING AT COMPOSITE WASSERMANN CURVES

The syphilologist is aware that, at a given stage of the infection, the course of the Wassermann reaction during treatment is more or less uniform, and many rules of thumb have accumulated. For example, Wassermann fastness is common in late congenital or osseous syphilis; the test tends rapidly to become negative in seropositive

[1] From the Medical Clinic of the Johns Hopkins Hospital.

[2] Moore, J. E., and Keidel, A.: The Treatment of Early Syphilis. I. A Plan of Treatment for Routine Use. *J. H. Hosp. Bull.*, xxxix, No. 1, p. 1.

[3] Keidel, A., and Moore, J. E.: The Wassermann Reaction in the Johns Hopkins Hospital. *J. H. Hosp. Bull.*, 1923, xxxiv, 16.

primary syphilis; continued Wassermann negativity is frequent in certain neurosyphilitics. Some years ago it occurred to us[4] that a true picture of the course of the test during treatment in different types of syphilitic infection might be obtained if one could strike an average for a large number of patients. It seemed feasible from a statistical standpoint to arrive at such an average by making use of the numerals in common use in Wassermann phraseology. Thus in most laboratories, four plus, or more briefly 4, signifies complete fixation of complement and a strongly positive test; 3 indicates 75 per cent fixation; 2, 50 per cent, or a doubtful result; 1, almost complete hemolysis; and 0, complete hemolysis or a negative result. We may indicate the course of the test in a given patient over a period of weeks by setting down a row of figures, thus, 444200. In this instance, one sees at a glance that during the first three weeks of treatment, the Wassermann remained completely positive; by the fourth week it was doubtful; and by the fifth and subsequent weeks it had become frankly negative.

The next step is to set down, one under the other, the numerical values for the Wassermann for a series of patients, add the figures in each separate column, and divide each total by the number of cases in that column. Such an average result may then be plotted on an ordinate-abscissa chart and an easily visualized graphic result obtained. So far as we know, this statistical method has not been applied to a study of the Wassermann reaction by other investigators.

DESCRIPTION OF CASE MATERIAL

We have adopted this method in 879 cases of early syphilis. This is more than double the number of cases reported on from the clinical standpoint in the second paper of the series,[5] but the fact that in the 879 cases now under consideration the clinical outcome is often unknown (usually because the patient has been lost from sight) does not militate against the value of the material from many points in con-

[4] Moore, J. E.: Studies on the Influence of Pregnancy in Syphilis. I. The Course of Syphilitic Infection in Pregnant Women. *J. H. Hosp. Bull.*, 1923, xxxiv, 89.

[5] Moore, J. E., and Kemp, J. E.: The Treatment of Early Syphilis II. Clinical Results in 402 Patients. *J. H. Hosp. Bull.*, xxxix, No. 1, p. 10.

nection with the course of the Wassermann reaction. These cases have been drawn from a total of more than 2500 patients with early syphilis and are selected in only one particular, namely, that the patient must have received at least four injections of arsphenamin (therefore having four consecutive Wassermann records) at fairly regular intervals. Thus, also, quite a number of patients available for discussion from the clinical standpoint, since they had been restudied several years after three or less doses of arsphenamin, could not be utilized in the present study.

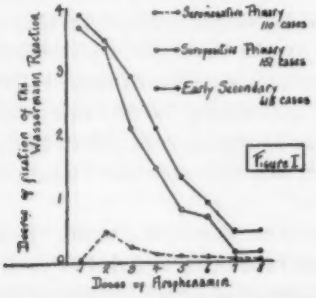

FIG. I. THE COMPOSITE WASSERMANN CURVE FOR SERONEGATIVE PRIMARY AND SEROPOSITIVE PRIMARY, AND FOR EARLY SECONDARY SYPHILIS, DURING THE FIRST COURSE OF WEEKLY INJECTIONS OF ARSPHENAMIN

COMPOSITE WASSERMANN CURVES DURING FIRST COURSE OF ARSPHENAMIN

In Figure I are shown composite Wassermann curves for 110 cases of seronegative primary, 151 cases of seropositive primary, and 618 cases of early secondary syphilis, during the first course (8 injections) of arsphenamin. The first point in each curve indicates the composite Wassermann before any treatment. This point is less than 4, both for seropositive primary and early secondary syphilis, because in a few patients the test was not completely positive before treatment was instituted. In the seronegative primary group, there is an interesting provocative rise in the curve immediately following the first injection of arsphenamin. Eighteen, or 16.3 per cent, of the 110 patients, developed some degree of Wassermann fixation within a

week after the first arsphenamin treatment, and in 9 of these the test became completely positive. The average duration of infection was here a few days longer than in the 92 instances in which the Wassermann remained completely negative, and the patients were on the verge of developing a positive test. Following this initial rise, the curve rapidly sinks back toward negative, which is reached by the seventh week of treatment.

In the seropositive primary and early secondary groups, the provocative phenomenon is absent, because in the vast majority of patients the test was completely positive at the outset. However, in 57 cases of early secondary syphilis in which the initial test showed less than complete fixation, such an increase in titre occurred after the first arsphenamin injection in 31, or 54.3 per cent. If our Wassermann tests had been quantitatively titrated, the same phenomenon would probably have been found more frequently.

The composite curves in these two groups progress toward negative in an interesting fashion. Comparatively little effect is produced in one week by the first injection, but following this the drop becomes much more rapid until the seventh week, when it suddenly flattens out at a point almost but not quite negative. It is possibly significant that the degree of fall in the composite Wassermann curves is greatest for the first four injections, gradually decreasing with later treatments. It is suggested that these phenomena may indicate a gradually increasing tolerance to arsphenamin on the part of *T. pallidum*, with the development of drug fastness.[6] Unfortunately, we have not exceeded an eight injection course of arsphenamin, so that we have no information as to whether this apparent decrease in effectiveness is prolonged further. The response obtained by an eight injection course is, however, sufficiently satisfactory in the average case as to make it seem unnecessary to administer further arsphenamin before shifting to

[6] We cannot corroborate the results of Silberstein (Zur Frage der Salvarsanresistenten Lues, *Arch. f. Derm. u. Syph.*, 1924, cxlvii, 116), who believes that a resistant strain of *T. pallidum* is gradually developing. He finds that in recent years the Wassermann reaction in early syphilis is less rapidly influenced by arsphenamin treatment than formerly. Our material extends over a period of 10 years, and we see no serologic indication that treatment is less effective now than in 1917 and earlier.

mercury. We except from this rule a few patients in whom complete Wassermann fixation is still present at the end of eight doses of arsphenamin. Partly for experimental reasons, we have recently adopted the routine of prolonging the first arsphenamin course in these patients to 10 or 12 injections.

EFFECT OF ARSPHENAMIN ON THE BLOOD WASSERMANN REACTION

Individual cases of early syphilis show considerable variation in the rapidity with which the Wassermann reaction becomes and remains negative. In a minority, a negative result persisting throughout the first course of treatment is obtained with surprising rapidity, two

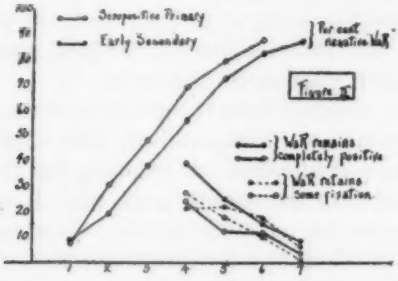

FIG. II. THE INFLUENCE OF REPEATED INJECTIONS OF ARSPHENAMIN ON THE WASSERMANN TEST

The ordinate represents percentage incidence; the abscissa, the number of arsphenamin injections.

injections of arsphenamin sufficing to bring about this result in 31.4 per cent of seropositive primary and in 19.5 per cent of early secondary cases. Figure II shows that in both groups, a negative Wassermann may be expected as the result of a single course of arsphenamin in approximately 85 per cent of all cases. From these curves, it appears that for the average patient the optimal number of arsphenamin injections in the first course of treatment should be from six to eight.

It should be emphasized that these composite curves are based on weekly injections of arsphenamin in average doses of 0.4 gm. for men and 0.3 gm. for women. We have no comparative information as to the effect of neoarsphenamin, or other arsphenamin products, on the composite Wassermann curve.

CORRELATION OF CLINICAL OUTCOME AND WASSERMANN DATA

In the preceding paper[5] we have classified the clinical outcome in early syphilis into six groups, namely, probable cure, recurrent secondary syphilis, neurorecurrences, late syphilis (tertiary including cardiovascular), neurosyphilis, and latent syphilis. In order to illustrate certain points in connection with the Wassermann reaction, it is necessary briefly to discuss the ultimate clinical outcome in special groups of cases, but without emphasis on the amount of treatment administered or the length of observation. As to the latter point, it need only be said that except in the cases of recurrent secondary syphilis or neurorecurrences, all patients have been followed for at least one

TABLE I

Clinical outcome in patients with early syphilis, included in present series from standpoint of blood Wassermann

STAGE OF INFECTION	CLINICAL OUTCOME KNOWN. TOTAL CASES	PER CENT FALLING INTO GROUPS OF				
		Cure	Recurrent secondary syphilis	Neuro-recurrence	Late syphilis (tertiary, C.V., C.N.S.)	Latent WaR late (P.E. negative)
Primary seronegative.....	34	19 (55.8%)	5 (14.7%)	1 (2.9%)	4 (11.7%)	5 (14.6%)
Primary seropositive.....	51	19 (37.2%)	5 (9.8%)	1 (1.9%)	8 (15.6%)	18 (35.2%)
Early secondary.....	169	51 (30.1%)	22 (13.0%)	12 (7.1%)	26 (15.3%)	58 (33.6%)

year, usually longer, following the completion of treatment. The clinical outcome is known in 254 of the 879 cases utilized in this paper, and these data, presented in Table I, will serve for comparison with the special points presently to be discussed. The fact that 55.8 per cent of patients with seronegative primary syphilis are regarded as probably cured, as contrasted with 37.2 per cent of those with seropositive primary and 30.1 per cent of the early secondary group, again emphasizes the extreme importance of early treatment.

COMPOSITE WASSERMANN CURVE DURING PROLONGED TREATMENT

In order to examine the subsequent course of the Wassermann reaction, we have selected 50 patients with early secondary syphilis, all of whom received continuous treatment of four or more courses of arsphenamin with interim mercury and potassium iodide. The record of each patient includes at least 24 separate Wassermann tests performed over a period of about one year. The average time devoted to mercurial treatment was approximately six weeks for the first course, eight weeks for the second, and twelve weeks for the third. The composite Wassermann curve of these 50 patients is presented in

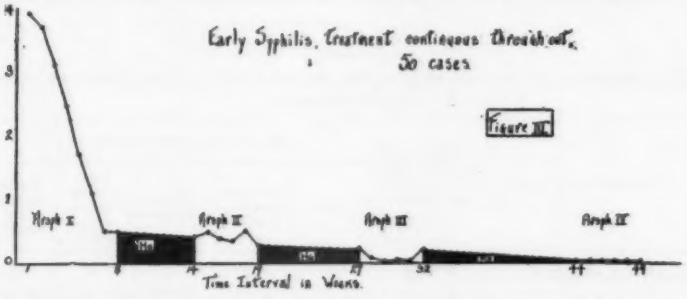

FIG. III. THE COMPOSITE WASSERMANN CURVE OF 50 PATIENTS WITH EARLY SECONDARY SYPHILIS, TREATED CONTINUOUSLY FOR FOUR COURSES OF ARSPHENAMIN PLUS INTERIM MERCURY

In this and subsequent charts, the ordinate represents, as in Figure I, the degree of fixation of the Wassermann reaction; the abscissa, the element of time, or the number of arsphenamin injections.

Figure III. Attention is directed to the fact that during the periods of mercury therapy there was no increase in Wassermann titre, but that, on the contrary, the curve tends slightly further toward negative. For all practical purposes, all trace of Wassermann fixation has disappeared by the third course of arsphenamin (the 28th week of treatment). The subsequent clinical outcome, after one or more years of observation without treatment, is known in 21 of these 50 patients. In not a single instance was there a clinical recurrence of the secondary type, nor a Wassermann recurrence. Twenty, or 95 per cent, are regarded as probably cured; one has central nervous system syphilis.

This is a striking demonstration of the efficacy of continuous treatment, prolonged for at least one year.

INTERMITTENT VERSUS CONTINUOUS TREATMENT: EVIDENCE PROVIDED BY COMPOSITE WASSERMANN CURVES

Our next step is to determine what contrast, if any, exists in the course of the Wassermann reaction in patients subjected to continuous antisyphilitic treatment by our routine of alternating courses of arsphenamin and mercury, as compared with a series of similar cases in which treatment was intermittent, consisting of one or more courses of arsphenamin, sometimes followed by mercury, sometimes not, but always with a period without treatment before the subsequent arsphenamin

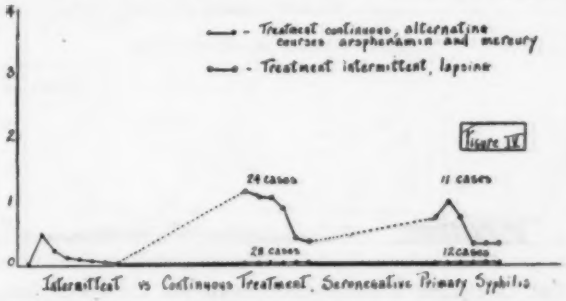

FIG. IV. THE COMPOSITE WASSERMANN CURVE OF SERONEGATIVE PRIMARY SYPHILIS: INTERMITTENT VERSUS CONTINUOUS TREATMENT (SEE TEXT)

course. In this series, the lapse or rest period was involuntary on our part, and due to lack of cooperation on the part of the patient. Nevertheless, the material roughly parallels that intentionally treated by the intermittent system, periods of treatment alternating with periods of rest. Composite curves showing this comparison for seronegative primary syphilis as one group, and for the combined seropositive primary and early secondary cases as another, are presented in Figures IV and V. In order to bring out the contrast more strongly, the period of mercurial therapy in the continuously treated groups has been represented as occupying the same time interval as the lapse or rest period in the groups with intermittent treatment, though it was actually much shorter. To give the lapsed intervals their proper

space relation on the chart would unnecessarily increase its size. In each chart the course of the Wassermann reaction in those patients treated continuously is progressively toward negative. In the seronegative primary patients treated continuously, the test has become negative by the last arsphenamin injection of the first course and remains so permanently thereafter. The curve of the regularly treated seropositive primary and early secondary groups is almost an exact duplicate of Figure III, showing a similar curve for 50 selected patients.

The Wassermann curve in the groups receiving lapsing or intermittent treatment is in striking contrast. During every interval

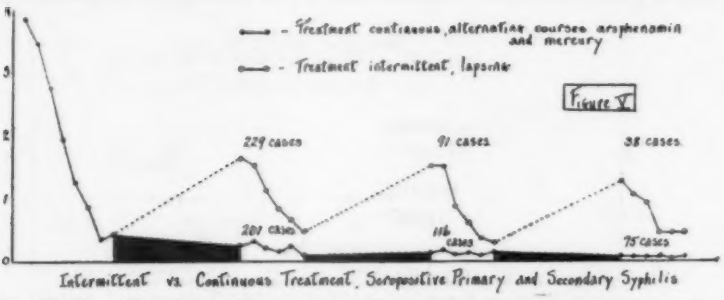

FIG. V. THE COMPOSITE WASSERMANN CURVE FOR COMBINED SEROPOSITIVE PRIMARY AND EARLY SECONDARY SYPHILIS: INTERMITTENT VERSUS CONTINUOUS TREATMENT

without treatment, the Wassermann reaction tends to recur toward positive, and in a sufficiently large number of patients to bring the compositive curve well up on the scale. Moreover, the response of the test to the second arsphenamin course is not so prompt as from the first, and tends to become even less in subsequent courses. The rise toward positive is almost as great during each lapse from treatment. These curves, based on actual experience, are close duplicates of the theoretical curves of response to continuous and intermittent treatment, presented in the first paper of this series.[2]

Figures showing the number of patients on which these curves are based are presented in Table II. We have tabulated as recurrent positive Wassermanns all cases in which the test, having been reduced

to doubtful, suggestive negative, or negative (2, 1, or 0) during the first course of treatment, showed 75 per cent or more fixation (3 or 4 plus) at the start of the second course. This excludes those instances in which the Wassermann, remaining completely or partially positive during the first course, showed the same degree or less of fixation at a subsequent date. When a lapse in treatment, lasting an average of 7½ months, occurred between the first and second arsphenamin courses, recurrent positive Wassermanns were 10 times as frequent as when

TABLE II

Intermittent versus continuous treatment: the incidence of Wassermann recurrences

		Interval between courses of arsphenamin occupied by					
		Continuous mercury therapy			Lapse in treatment (average duration 7½ months)		
		Total cases	Number with recurrent WaRs	Per cent of WaR recurrence	Total cases	Number with recurrent WaRs	Per cent of WaR recurrence
Two courses of arsphenamin	Seronegative primary	28			24	8	33.3
	Seropositive primary and early secondary	201	7	3.4	229	71	31.0
Three courses of arsphenamin	Seronegative primary	12			11	2	18.1
	Seropositive primary and early secondary	116	4	3.4	91	33	35.8

treatment was continued without interruption. Furthermore, clinical recurrences of a secondary type developed in 30, or 11.8 per cent, of patients treated intermittently, as contrasted with only 6, or 2.6 per cent, of those who received two courses of arsphenamin separated by mercury. A lapse between the second and third treatment courses was also attended by a ten-fold incidence of Wassermann recurrences.

INTERMITTENT VERSUS CONTINUOUS TREATMENT: THE ULTIMATE CLINICAL OUTCOME

On the basis of ultimate clinical outcome, too, there can be shown convincing differences between the two types of treatment. These

data are presented in Table III. Under the head "two courses" are included in the continuous group all patients who faithfully carried out mercury therapy between the first and second courses of arsphenamin, whether or not there was a later lapse in treatment; while in the lapsing group are placed those patients who, though some of them took some mercury, allowed an average interval of 7 months without treatment to elapse between the first and second arsphenamin courses. The same classification is followed in the "three course" division. It must be repeated that the clinical classification of these patients is based (except for recurrent secondary syphilis and neurorecurrences), not on the patient's status immediately after a lapse in treatment, but on his ultimate condition one or several years follow-

TABLE III

Intermittent versus continuous treatment: the ultimate clinical outcome

TREATMENT		TOTAL NUMBER OF PATIENTS	CURE	RECURRENT SECONDARY SYPHILIS	NEURORECURRENCE	LATE SYPHILIS (TERTIARY, C.V., C.N.S.)	LATENT SYPHILIS (WaR RECURRENCE)
Two courses	Continuous	69	43 (62.3%)	4 (5.8%)	2 (2.9%)	10 (14.4%)	10 (14.4%)
	Lapsing	112	21 (18.8%)	23 (20.5%)	7 (6.2%)	12 (10.7%)	49 (43.7%)
Three courses	Continuous	29	24 (82.7%)		1 (3.4%)	3 (10.3%)	1 (3.4%)
	Lapsing	36	10 (27.7%)	4 (11.1%)	1 (2.7%)	6 (16.6%)	15 (41.6%)

ing the last date of any treatment. Probable cure is three times as frequent in patients who received continuous treatment as in those treated intermittently; while the reverse is true of recurrent secondary or latent syphilis. Subsequent observation will probably transfer many of the patients with latent syphilis into the groups with various late manifestations of the disease.

The frequency of early clinical and Wassermann recurrences and the paucity of clinical cures in patients treated intermittently as compared with the opposite state of affairs in those treated continuously cannot be explained wholly by the fact that the former group received

little or no mercury and the latter a great deal. The explanation lies rather in the relation of antisyphilitic treatment to the patient's own defense mechanism. In early syphilis, treatment with powerful treponemicidal drugs is ordinarily begun at a point when the patient has either developed no generalized resistance against the infection, or is just beginning to develop it. Under these conditions, arsphenamin does for him what he otherwise (if untreated) would succeed in doing for himself, namely, heal lesions and destroy large numbers of organisms. If by accident or design he stops treatment before the time when theoretically every organism is destroyed, he is left in the same position as to his immune processes as if he had freshly acquired the disease, and is subject to immediate clinical or Wassermann recurrences. That these may occur with a high degree of frequency is amply illustrated by our material. If this much is admitted, it follows that since the patient is not allowed to make use of his own defense mechanism, antisyphilitic treatment must accomplish the suppression and eradication of organisms. In order to attain this result, it is necessary that no opportunity for multiplication and possible redissemination of organisms be allowed and that at every moment until the last organism is dead, or permanently walled off, the patient must be under the influence of a treponemicidal drug. This can be accomplished only by some such routine of continuous treatment as we have outlined.

Throughout these papers we emphasize the fact that our statements apply to early syphilis. Later in the course of the disease, the situation is quite different. Maximal resistance against the infection has already been developed; organisms are usually walled off in more or less inaccessible foci; and antisyphilitic treatment no longer so greatly disturbs the delicate process of maintenance of resistance. Under these circumstances, we have formed the impression, though we have not as yet subjected our material to careful analysis, that it makes little difference in the end result whether treatment is continuous, intermittent, or indeed follows any set plan. Individualization is now possible, whereas in early syphilis it is unwise and unnecessary.

VARIATIONS FROM THE "AVERAGE" COMPOSITE WASSERMANN CURVE

There are two interesting deviations from the average Wassermann response of seropositive primary and early secondary syphilis, shown in Figure I. In an appreciable number of patients, the blood Wassermann fails to become negative with the average rapidity, retaining complete or partial fixation throughout a 6 to 8 injection course of arsphenamin. About an equal proportion show the reverse state of affairs, in which the test becomes and remains negative after one or two injections of the drug. These variations from the average are worthy of further analysis.

PERSISTENT WASSERMANN POSITIVITY

In 17 patients, or 11.2 per cent of those with seropositive primary syphilis, and in 92, or 14.8 per cent of the early secondary group, the blood Wassermann retained complete or partial fixation after 6 injections of arsphenamin. The test remained completely positive in 10 of the seropositive primary and 60 of the early secondary patients. The cause of a persistently positive Wassermann reaction early in the course of a syphilitic infection is imperfectly understood. On clinical grounds, at least, it cannot be attributed, as is so often possible in later stages of the disease, to osseous, visceral, or cardio-vascular syphilis. Some instances are due to early involvement of the nervous system, and we have already pointed out[7] the higher incidence of abnormal spinal fluids in this group of patients than in the average early syphilitic. Figure VI shows the composite curve of the 109 patients with persistent Wassermann fixation during the first course of treatment, as compared with all remaining cases of seropositive primary or early secondary syphilis. In the persistently positive Wassermann group, the curve for the second, third, and fourth courses of arsphenamin is based on 44, 15, and 12 cases, respectively. In order to ensure strictly comparable curves in the two groups, only those cases are utilized in which treatment was continuous with no lapses. When

[7] Moore, J. E.: Studies in Asymptomatic Neurosyphilis. II. The Classification, Prognosis, and Treatment of Early Asymptomatic Neurosyphilis. *J. H. Hosp. Bull.*, 1922, xxxiii, 231.

the special group is excluded, the Wassermann becomes almost completely negative by the end of the first course of treatment, and remains so throughout the period of observation. In the special group, on the contrary, a completely negative composite test is approached only during the fourth course of arsphenamin, an appreciable degree of fixation being retained throughout. In other words, when this special group of patients is eliminated, the test promptly becomes and remains negative.

Judging by these curves alone, one might be led to believe that, in general, a persistently positive test throughout the early part of treatment means more difficulty in obtaining ultimate cure than when the test becomes negative at the average rate. From the standpoint

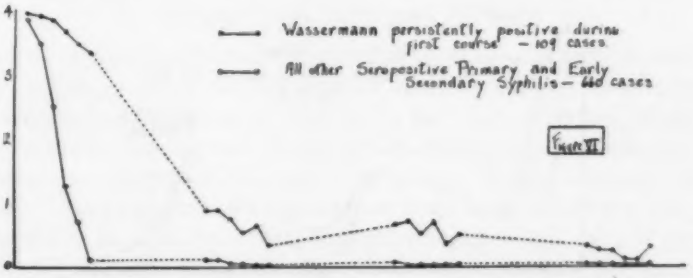
Wassermann persistently positive during first course — 109 cases
All other Seropositive Primary and Early Secondary Syphilis — 440 cases
FIGURE VI.

FIG. VI. THE COMPOSITE WASSERMANN CURVE FOR SEROPOSITIVE PRIMARY AND EARLY SECONDARY SYPHILIS, WHOSE BLOOD WASSERMANNS RETAIN ALMOST COMPLETE FIXATION THROUGH THE FIRST ARSPHENAMIN COURSE, AS COMPARED WITH ALL REMAINING EARLY CASES IN WHICH THE WASSERMANN BECOMES NEGATIVE WITH AVERAGE RAPIDITY

of ultimate clinical outcome, however, this impression is not wholly borne out. Clinical data are available in 34 patients with fixed Wassermanns during a single course of treatment, and these figures may be compared with the clinical results in all other seropositive primary and early secondary cases. The special group shows a considerable variation from the standard in only one particular, namely, a 23.5 per cent incidence of late syphilis, as contrasted with 13.9 per cent in the standard group. The material is so small as to make it profitless to carry further the investigation or to venture an interpretation of the significance of this result. It is recorded with the hope that further study may produce information of value.

"PREMATURELY NEGATIVE" WASSERMANNS

In 117 patients with seropositive primary or early secondary syphilis in whom the Wassermann was completely positive before treatment, the test became and remained negative following one or two doses of arsphenamin. This occurred in 36 patients following a single injection and in 82 after two injections. As compared with the average Wassermann course, the test may be said to have become prematurely negative. The composite Wassermann curve of these 117 patients, as contrasted with all remaining seropositive early syphilis, is shown in Figure VII. Here, in order to bring out more clearly the point in question, the curves during the second and third courses of arsphenamin are based on lapsing or intermittent treatment rather than on

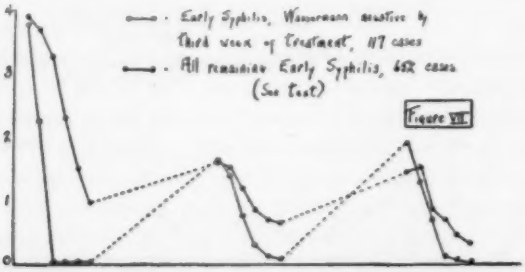

FIG. VII. THE COMPOSITE WASSERMANN CURVE FOR SEROPOSITIVE PRIMARY AND EARLY SECONDARY SYPHILIS, WHOSE BLOOD WASSERMANNS BECOME "PREMATURELY NEGATIVE," AS CONTRASTED WITH ALL REMAINING EARLY CASES (SEE TEXT)

continuous therapy. The curve for the second arsphenamin course represents 30 patients of the prematurely negative group and 199 of the remaining early cases; that for the third course, 18 and 73 cases, respectively. The tendency for the blood Wassermann to become prematurely negative during the first course is perpetuated in subsequent courses. Even after a clinical or Wassermann recurrence, which occur with considerable frequency in this special group, there is some factor inherent in the response of the patient to infection and treatment which causes his blood Wassermann to become negative with more rapidity than in the average early case.

In this special group of patients, the Wassermann reaction may be a partial index of the patient's resistance against infection; and the rapidity with which reagin disappears from the blood may presage a low grade of immunity or resistance, as compared with the average case. With this point in mind, we have studied the ultimate clinical outcome in the special group under discussion as compared with all remaining seropositive primary and early secondary syphilis. These data bring out a significant difference in the incidence of recurrent secondary syphilis. Redissemination of organisms and clinical recurrences of a secondary type occur four times as frequently in the prematurely negative Wassermann group (30.5 per cent) as in the average patient whose Wassermann response to treatment is less rapid (8.6 per cent).

SERONEGATIVE SECONDARY SYPHILIS

In this connection, we have also studied those cases of early secondary syphilis in which the Wassermann reaction was not completely positive before treatment, in spite of the fact that outspoken lesions were present. Among our 618 patients the Wassermann test was positive before treatment in 561, or 90.77 per cent. A suggestive positive result (75 per cent fixation) was obtained in 24 cases, or 3.89 per cent; doubtful in 14, or 2.26 per cent; suggestive negative in 11, or 1.77 per cent; and the test was frankly negative in 8 cases, or 1.29 per cent: a total of 57 patients in whom the Wassermann showed incomplete fixation before any treatment. The explanation of this failure of the test to become completely positive cannot be related to the type or extent of early lesions present, since rashes and mucous lesions were as frequent and as profuse as in the frankly positive group. Nor is it due to the influence of sex,[4] since the cases are equally divided between males and females, and but 7 of the 25 females were pregnant at the time of admission. This type of Wassermann response depends, we believe, on the same factors responsible for the "prematurely negative" Wassermann group just discussed, namely, an inherent lack of resistance against infection, with a different type of biologic response to the presence of the organism than in the average case.

The number of cases at our disposal is here insufficient to permit charting a composite Wassermann curve covering the whole period of treatment, as in the preceding instances. The composite chart for

the first course of arsphenamin, as compared with all other early secondary cases, is shown in Figure VIII. A provocative reaction following the first arsphenamin injection is clearly apparent. In addition, the test becomes almost completely negative by the fourth week, three weeks earlier than in the standard group. It is probable that the same factor is responsible both for the failure of the Wassermann to become completely positive before treatment and for the abnormally rapid response to arsphenamin.

In 20 of the 57 cases in this special group the ultimate clinical outcome is known, and may be compared with the results in the more usual Wassermann positive secondary syphilis. Under similar

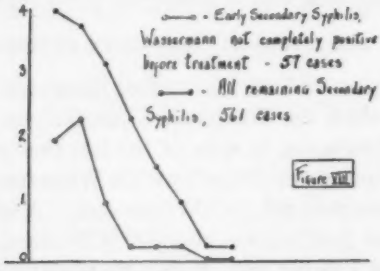

FIG. VIII. THE COMPOSITE WASSERMANN CURVE OF 57 PATIENTS WITH EARLY SECONDARY SYPHILIS, WHOSE BLOOD WASSERMANNS WERE NEGATIVE OR INCOMPLETELY POSITIVE BEFORE TREATMENT, AS COMPARED WITH ALL CASES IN WHICH THE TEST WAS COMPLETELY POSITIVE BEFORE TREATMENT

conditions of treatment, recurrences of a secondary type are five times as frequent in the special (45 per cent) as in the standard group (8.7 per cent).

This difference may be further emphasized by pointing out that among 169 patients with early secondary syphilis, recurrent secondary lesions appeared in 22, or 13.0 per cent. Fifty-one of the total number of early secondary patients fall into one or other of the special groups just discussed, that is, with "prematurely negative" Wassermanns after treatment or with incompletely positive tests before treatment. The incidence of recurrent secondary lesions in these 51 cases is 29.4 per cent (15 cases), while a similar course of events occurred in only 7, or 5.9 per cent, of the remaining 118 early secondary cases.

On the basis of these results, we believe that an incompletely positive Wassermann test in early secondary syphilis, or a test which is reduced to negative by one or two injections of arsphenamin, has considerable prognostic value. It is suggested that these types of Wassermann response indicate an inability of the body to react to the presence of *T. pallidum* by the usual defensive processes, and that a lapse in treatment is likely to be followed by a redissemination of organisms with the possibility of involvement of important structures which may have escaped the first generalization. In such cases it is even more essential than usual that treatment be intensive and continuous, so that treponemicidal drugs may accomplish the destruction of organisms which the patient is unable to deal with himself.

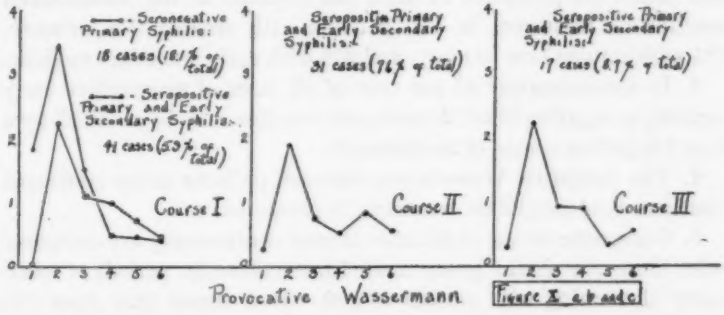
Seronegative Primary Syphilis: 18 cases (16.1% of total)
Seropositive Primary and Early Secondary Syphilis: 41 cases (53% of total)
Course I
Seropositive Primary and Early Secondary Syphilis: 31 cases (74% of total)
Course II
Seropositive Primary and Early Secondary Syphilis: 17 cases (8.7% of total)
Course III
Provocative Wassermann
Figure X a b and c

FIG. IX. THE PROVOCATIVE WASSERMANN AS ILLUSTRATED BY COMPOSITE WASSERMANN CURVES

THE PROVOCATIVE WASSERMANN REACTION

One final point is brought out by our method of study of the Wassermann reaction, namely, the strong probability of the existence of a true provocative Wassermann. We have already shown that the provocative phenomenon was present in 16.3 per cent of all patients with seronegative primary syphilis (Figure I), and in 54.3 per cent of the seropositive primary and early secondary cases with incomplete Wassermann fixation before treatment (Figure VIII). The composite in all the patients of these two groups who showed the provocative phenomenon is charted in Figure IX. An increase of about 50 per cent on the scale of 4 followed the first injection of arsphenamin in each

group. The same type of response occurs in about 8 per cent of all early patients receiving two or three courses of the drug, more frequently, of course, after lapsing than after continuous treatment. It is surely significant that this increase in Wassermann titre always occurs after the first, and not after subsequent injections of an arsphenamin course.

SUMMARY

1. A statistical method is described which permits the charting of the average blood Wassermann response to treatment of a large series of syphilitic patients.

2. This method is applied to 879 cases of early syphilis; and charts and tables are presented to show the response of the Wassermann reaction to treatment in 110 patients with seronegative primary. 151 with seropositive primary, and 618 with early secondary syphilis.

3. In approximately 85 per cent of all cases of seropositive early syphilis, a negative blood Wassermann reaction may be obtained by a 6 to 8 injection course of arsphenamin.

4. The composite Wassermann curve of patients under prolonged continuous antisyphilitic treatment is presented.

5. Composite curves of patients treated continuously are compared with those of a similar group treated intermittently, periods of treatment alternating with periods of rest. It is shown that from this standpoint continuous treatment is productive of greatly superior results.

6. An attempt is made to correlate these serologic data with the ultimate clinical outcome. From this standpoint, also, continuous treatment produces better results than intermittent treatment.

7. It is shown that in a certain number of patients with early syphilis, the response of the blood Wassermann to treatment may be, as compared with the average, abnormally rapid or abnormally delayed. Curves are presentd to show these variations from the average.

8. An analysis of the material suggests that frequent repetition of the Wassermann test during treatment is of considerable prognostic value. Data are provided which further suggest that a "prematurely

negative" Wassermann test may indicate a lack of resistance to syphilitic infection on the part of the patient.

9 A study of seronegative secondary syphilis leads to this same tentative conclusion, and indicates that a negative Wassermann in untreated secondary syphilis is an index of lack of resistance.

10. The applicability of the composite Wassermann curves to the problem of the provocative Wassermann reaction is pointed out.

IRRADIATED ORANGE JUICE

Its Value as an Antirachitic Agent[1]

HERMAN L. MASLOW, DAVID H. SHELLING,[2] AND BENJAMIN KRAMER

From The Harry Caplin Pediatric Research Laboratory, The Jewish Hospital of Brooklyn, N. Y.

It has been conclusively shown that substances which are not capable of preventing or curing rickets may acquire antirachitic properties when exposed to ultraviolet light. The studies of Hess and Weinstock (1), confirmed by others (2), indicate that cholesterol and phytosterol, and presumably substances containing these ingredients, may be endowed with antirachitic potency by irradiation, so that when fed to rats, along with a rickets-producing diet, the animals fail to develop the disease. Kramer (3), Cowell (4), and György (5) have shown that irradiated cow's milk will cure rickets when fed to rachitic children; and Steenbock (6) obtained similar results with rats.

The possibility of producing an agent which besides being antiscorbutic would also be capable of preventing or curing rickets centered our attention on irradiated orange juice, since it has been shown by Zilva (7) that irradiation of lemon juice for as long as eight hours does not impair its antiscorbutic potency. Our experiments were therefore concerned with the cure of experimentally produced rickets in the rat by administering irradiated orange juice along with a standard rickets-producing diet.

EXPERIMENTAL

Twenty-eight rats, all of about the same age (25 to 28 days) and nearly of the same weight (25 to 35 grams) were divided into four groups and kept on a rickets-producing diet for 25 to 28 days. Two groups received McCollum's diet No. 3143 (8), and the remaining two groups were fed Steenbock's diet No. 2965 (9). All the animals were

[1] Received for publication May 17, 1926.

[2] Harry Caplin Research Fellow.

kept in a dimly lit room. At the end of this period groups I and III received irradiated orange juice for from 5 to 15 days. Groups II and IV were used as controls and received non-irradiated orange juice. At the expiration of the experimental period the animals were weighed, anaesthetized and bled to death. The organs were examined grossly, special attention being paid to the long bones and thorax. Thin sections of the upper part of the tibiae were immersed in 1 per cent silver nitrate and examined under the dissecting microscope for the presence or absence of healing as evidenced by the "line test" (10). Blood phosphorus determinations were made at once on the serum of most of the animals.

The orange juice used in our experiment is a commercial product known as "Mission Orange Juice." The manufacturers informed us that it is made by grinding peeled oranges and then concentrated by partial evaporation. On analysis it was found to contain 0.12 per cent oils and fats and 0.31 per cent ash. This concentrated juice was mixed with two parts of distilled water and then divided into two portions, one of which was irradiated for three hours under a mercury vapor quartz lamp at a distance of 18 inches. The finished product was kept on ice and fed to the animals daily in quantities averaging about 15 cc. per animal per day.

RESULTS

The accompanying table shows that, when rachitic animals are fed irradiated orange juice, healing may be present after five days and is almost complete at the end of fifteen days. Those fed on non-irradiated orange juice showed either no healing or only small deposits of calcium salts in places about the cartilage cells, but none in the metaphysis.

The inorganic phosphorus of the serum in the majority of the animals was higher in those receiving irradiated orange juice than in the controls. Serum calcium determinations were not made, but we may assume, from previous studies of Howland and Kramer (11) and others (12), that in experimental rickets produced by feeding a diet high in calcium and low in phosphorus the serum calcium is about 10 mg. per 100 cc. in the control animals as well as in those treated with various antirachitic agents. This calcium

TABLE I

DATE	RAT NUMBER	DIET	DAYS ON ORANGE JUICE	RICKETS	LIME TEST	HEALING	SERUM PHOSPHORUS	REMARKS
			Irradiated					
2/23/26	35	Steenbock	7 days		++++	Beginning	4.1	
2/23/26	36	Steenbock	7 days		*2(++++)	Marked		
2/23/26	37	Steenbock	7 days		2(++++)	Marked	4.6	
2/23/26	39	Steenbock	7 days		2(++++)	Marked		
			Non-irradiated					
2/23/26	38	Steenbock	7 days	++++	None	None	2.6	
2/23/26	43	Steenbock	7 days	++++	None	None		
2/23/26	42	Steenbock	7 days	++++	None	None	2.5	
2/23/26	49	Steenbock	7 days	++++	None	None		
			Irradiated					
4/9/26	50	Steenbock	10 days		3(++++)	Marked		Healing in these rats occurred in osteoid metaphysis and not in ends of cartilage
4/9/26	53	Steenbock	10 days		3(++++)	Marked	2.6	
4/9/26	51	Steenbock	10 days		3(++++)	Marked	2.7	
4/9/26	52	Steenbock	10 days		3(++++)	Marked		
			Non-irradiated					
4/9/26	54	Steenbock	10 days	++++	None	None	2.8	
4/9/26	56	Steenbock	10 days	++++	None	None		
4/9/26	57	Steenbock	10 days	++++	None	None		
			Irradiated					
4/29/26	69	Steenbock	5 days		++++	Moderate	—	

			Non-irradiated					
4/29/26	68	Steenbock	9 days	++++	+		2.0	
			Irradiated					
4/30/26	60	Steenbock	15 days		5(++++)	Complete	3.2	Bone practically normal
4/30/26	70	Steenbock	15 days		5(++++)	Complete		
			Non-irradiated					
4/30/26	66	Steenbock	15 days	++++	?	Very slight beginning	—	
			Irradiated					
3/23/26	1	3143	7 days		2(++++)	Marked	4.2	
3/23/26	2Y	3143	7 days		2(++++)	Very marked		
3/23/26	2	3143	7 days		2(++++)	Very marked	4.2	
3/23/26	4	3143	7 days		2(++++)	Marked		
			Non-irradiated					
3/23/26	3	3143	7 days	++++	+	Very slight beginning	3.5	Slight scattered calcification at ends of cartilage
3/23/26	9	3143	7 days	++++		None		
3/23/26	10	3143	7 days	++++		None		
3/23/26	11	3143	7 days	++++		Very slight beginning	3.6	No calcification in osteoid metaphysis.

* Numbers preceding (++++) designate the degree of calcification of metaphysis as compared to (++++) Line Test.

value and our phosphorus findings indicate that healing occurred at a Ca × P product above 30, as originally observed by Howland and Kramer (13). They have shown that in active rickets the product of the concentration of the calcium and the inorganic phosphorus of the serum expressed in mg. per cent is always below 30, and as soon as healing occurs this product invariably rises above 35. However, in one group of our animals to which orange juice was fed for a period of 10 days marked healing occurred at a serum phosphorus of 2.6, or presumably at a product of 26; while the control animals with active rickets and with no healing had a serum phosphorus of 2.8. On careful microscopic study of sections of the upper part of the tibiae of the animals of this group, it was found that healing did not occur regularly at the ends of the epiphyseal cartilage as is usually encountered. Instead, the healing was most pronounced in the middle of the osteoid metaphysis while the cartilaginous processes were almost free from calcification. A similar observation has been made by de Bosanyi (14) who also found a marked healing of rickets with a low serum phosphorus in animals treated with adrenalin. These findings, therefore, raise the question as to whether or not there are two types of healing in rickets, namely: (1) where the healing begins at the ends of the epiphyseal cartilage and spreads downwards into the osteoid metaphysis and is usually associated with an elevated serum phosphorus, and (2) where healing begins in the middle of the metaphysis and occurs at a relatively low serum phosphorus. This observation warrants further study.

CONCLUSIONS

The present experiments are of preliminary nature and only serve to demonstrate that: 1. Antirachitic properties can be imparted to orange juice by irradiation with the mercury vapor quartz lamp. 2. After feeding of irradiated orange juice to rachitic rats healing may be demonstrated as early as five days and is almost complete at the end of fifteen days.

Experiments are now in progress to ascertain: 1. The antirachitic value of irradiated orange juice in the cure of rickets in children. 2. The effect of irradiation on the antiscorbutic factor of orange juice at various reactions (pH). 3. The length of time during which irradiated orange juice retains its antirachitic properties.

REFERENCES

(1) HESS, A. F., AND WEINSTOCK, M.: *J. Biol. Chem.*, 1925, lxiii, 297.
IDEM: *Ibid.*, 1925, lxiv, 181.
HESS, A. F., WEINSTOCK, M., AND HELLMAN, D.: *Ibid.*, 1925, lxiii, 305.
(2) STEENBOCK, H., AND DANIELS, A.: *J. Am. Med. Assn.*, 1925, **84:** 1093.
STEENBOCK, H., AND BLACK, A.: *J. Biol. Chem.*, 1925, lxiv, 263.
ROSENHEIM, O., AND WEBSTER, T. A.: *Lancet*, 1925, i, 1025.
(3) KRAMER, B.: *Am. J. Dis. Child.*, 1925, xxx, 195.
(4) COWELL, S. J.: *Brit. Med. J.*, 1925, i, 594.
(5) GYÖRGY, P.: *Klin. Wchnschr.*, 1925, iv, 1118.
(6) STEENBOCK, H., HART, E. B., HOPPERT, C. A., AND BLACK, A.: *J. Biol. Chem.*, 1925, lxvi, 441.
(7) ZILVA, S. S.: *Biochem. J.*, 1919, xiii, 164.
(8) MCCOLLUM, E. V., SIMMONDS, N., PARSONS, H. T., SHIPLEY, P. G., AND PARK, E. A.: *J. Biol. Chem.*, 1921, xlv, 333.
(9) STEENBOCK, H., AND BLACK, A.: *Ibid.*, 1925, lxiv, 263.
(10) MCCOLLUM, E. V., SIMMONDS, N., SHIPLEY, P. G., AND PARK, E. A.: *Ibid.*, 1922, l, 5.
(11) HOWLAND, J., and KRAMER, B: *Trans. Am. Pediat. Soc.*, 1922, xxxiv, 204.
(12) HESS, A. F., AND UNGER, L. J.: *Am. J. Dis. Child.*, 1922, xxiv, 323.
(13) HOWLAND, J., AND KRAMER, B.: *Monatschr. f. Kindheilk.*, 1923, xxv, 279.
(14) DE BOSANYI, A.: *Am. J. Dis. Child.*, 1925, xxx, 780.

BOOK REVIEWS

Nervous and Mental Disorders from Birth through Adolescence. By B. SACHS AND LOUIS HAUSMAN. 861 pp. $10.00 (*Paul B. Hoeber, New York City, 1926.*)

The appearance of "Nervous and Mental Disorders from Birth through Adolescence" by B. Sachs and L. Hausman illustrates well the progress in neurology during the last twenty years. Dr. Sachs' first book "A treatise on nervous diseases of children," which appeared in a second edition in 1905 and has been translated into German and Italian editions, was one of the first presentations of the nervous diseases of childhood, and certainly the first which was sound and comprehensive. It has been widely used as an authoritative textbook in both America and Europe. This new book by Dr. Sachs and his present associate, Dr. Hausman, who was formerly instructor in neuroanatomy at the Johns Hopkins Medical School, is not a revised edition of the former book, but an entirely new presentation. Both in general arrangement and content it reflects the extraordinary advance of modern neurology. It is especially important for the clinical reader, however, that this achievement of being up-to-date is not merely a re-echo of the literature of the subject as in a number of recent neuropsychiatric books but, as is apparent from almost every page, is based on a wide and intensive experience with clinical cases.

The book is divided into five parts. The introductory first part contains a presentation of "The structure of the nervous system in its relation to function" and a chapter on "Methods of examination as a first aid to diagnosis." Part II contains the organic diseases of the nervous system, Part III the functional and toxic diseases and Part IV the endocrine disorders, vasomotor and trophoneuroses. Part V, dealing with mental conditions, is introduced by a chapter on the normal child and youth.

In a brief review it is not possible to do justice to the immense material covered in the book. The chapter on the functional anatomy of the nervous system gives an excellent survey of the subject in a concise form, which nevertheless allows for the description of many details in a very clear and instructive manner. The review of methods of examination as a first aid to diagnosis constitutes a small neurological compendium in itself.

In the clinical section, the chapters on Poliomyelitis, Syphilis of the nervous system, Meningitis and Encephalitis, Hereditary and Family affections and Chorea and choreiform diseases may be mentioned as particularly useful and masterly presentations. The development and training of the normal child and normal youth is described by Dr. Sachs in a healthy and commonsense manner, in agreeable contrast to a great deal of the modern literature on this subject. This chapter is followed by what one might call a brief intermezzo on "The Evils of Psychoanalysis." There Dr. Sachs emphasizes his position as a stern opponent of Freu-

dian doctrines. Whoever, like the present reviewer, has the feeling that the development of psychoanalysis has emphasized and suggested to the psychiatric clinician a number of problems of serious interest and concern, deserving of careful investigations, will have to consider that Dr. Sachs has probably had especial opportunities for observing the frequent unfortunate results of the crude application of psychoanalytic methods to young people. His reasons for this opposition to psychoanalysis are interesting and constitute a valuable contribution to a subject which is in dire need of frank and definite enlightenment from competent and critical clinical observers. Less convincing than Dr. Sachs' argumentation is his recommendation of the book by Wohlgemuth who has seen fit in his "Critical examination of psychoanalysis" to repeat the many jokes concerning psychoanalysis which originated years ago in the coffee houses of Vienna and have since travelled around the world. With regard to the list of outstanding neurological opponents of psychoanalysis one has to consider that Dr. Dana has written the preface to what is undoubtedly the best American book on psychoanalysis (also so regarded by Freud), Frink's "Morbid fears and compulsions;" that Dr. Dercum has offered for the war neuroses the therapeutically sterile theory of a neuropathy on a degenerative basis; that Dr. Schwab takes an eclectic point of view with regard to psychoneuroses, drawing on Freud, Janet and Babinski; that Strümpell has propounded his own theory of hysteria which, though not offensive, is certainly not enlightening. The last part of the book contains an outline of mental examination, and chapters on psychoneuroses, psychoses and mental retardation. The literary references throughout the book are authoritative and well chosen. For a future edition one might suggest the omission of the legal term insanity as a heading of the chapter on mental diseases, and perhaps a little fuller discussion of the complicated problem of the diagnosis and treatment of early schizophrenic conditions, which may have a resemblance not only to affective but also to a number of psychoneurotic and psychopathic developments. In recent years physicians have become more and more interested in neuropsychiatric conditions in childhood and early youth. The general practitioner who wishes not only to treat these patients, but also to examine them thoroughly and carefully (which is sometimes overlooked), will find this book not only valuable on his shelves, but also indispensable on his desk.

F. I. W.

William Crawford Gorgas. His Life and Work. By MARIE D. GORGAS AND BURTON J. HENDRICK. Illustrated. Pp. 345. $5.00. (*Lea & Febiger, Philadelphia, 1924.*)

No medical student and indeed no medical practitioner of the present day can afford to be ignorant of the life and work of Doctor Gorgas. The general public, too, must be interested in a career so distinguished and so fraught with good to humanity. For it is this Gorgas who has rid the world of one of its great curses—a curse which for centuries brought suffering and death to thousands; a curse which defeated De Lesseps in his great project of building the Panama Canal.

It is this Gorgas, who, accepting the discovery of Walter Reed and his heroic band said to Reed "If it is the mosquito, I am going to get rid of the mosquito." Reed smiled, "It can't be done," he said, and this was the prevailing opinion.

"They say we can't do it" remarked Gorgas, "perhaps we can't, but we shall try." So the curse of Yellow Fever was removed from the face of the earth—and America built the Panama Canal where France had failed so disastrously.

Burton Hendrick with the coöperation of Mrs. Gorgas vividly tells the story—and it is an inspiring story of a young doctor, determined, enthusiastic, patient, courteous, rising step by step from the lowest rank in the medical service of the Army to its highest position as Surgeon-General. William Crawford Gorgas stands as one of the greatest of the benefactors of mankind in company with Edward Jenner, Wm. T. G. Morton, Louis Pasteur, Walter Reed, and the others who have conquered pain and disease. Through his efforts the tropics of the world have been made habitable for white men; what he was and what he did is related in this book. "His indefatigable zeal will be blessed by generations yet unborn."

H. B. J.

Neuritis and Neuralgia. By WILFRED HARRIS. 410 pp. $4.00. (*Oxford University Press, 1926.*)

This is an especially valuable clinical treatise which covers a much broader field than the title would suggest. Sections are devoted to the different forms of multiple neuritis, to neuritis and neuralgia of the individual cranial and spinal nerves and to a number of obscure visceral neuralgias and vasomotor disturbances. Conditions which may simulate these affections, such as migraine, muscular rheumatism and tabes dorsalis, are briefly discussed. In addition, some space is devoted to the applied anatomy and physiology of the cranial nerves. The author's treatment of multiple neuritis is adequate but without especial originality, and it is in the discussion of the many obscure and troublesome neuralgias that the chief value of the book lies. These are classified as well as the present state of knowledge permits and the diagnosis and most effective treatment outlined. Harris has had a very large experience in this difficult field and speaks with authority. He has employed alcohol injections with success not only in trigeminal neuralgia, but in the more unusual types. His experience is summarized in this book which will be of value to every neurologist.

F. R. F.

Handbook of Diseases of the Rectum. By LOUIS J. HIRSCHMAN, M.C., F.A.C.S. With two hundred and fifty-two illustrations, mostly original, and five colored plates. Fourth Edition, Revised and Rewritten. 403 pp. $6.50. (*The C. V. Mosby Company, St. Louis, 1926.*)

The field of proctology is covered very thoroughly in this edition. The first chapter deals with anatomical relations and is followed by a second, which is rather unique in that all symptoms referable to the rectum and anus are enumerated and elaborated. The following chapters are taken up with the examination of patients,

the technique and use of local and sacral anaesthesia, their indications and contraindications. The various disorders are then taken up separately and presented in a clear and concise manner, the 252 excellent illustrations giving an additional clarity to the text. This book, although it does not take the place of a text for the student, should be of considerable assistance to the busy general practitioner.

W. D. N.

The Diagnosis and Treatment of Tuberculosis of the Hip. G. R. GIRDLESTONE, B.M. (Oxon), F.R.C.S. 94 pp. $2.50. (*Oxford University Press, 1925.*)

In this short monograph Girdlestone presents in a most delightful manner the clinical aspect of the diagnosis and treatment of tuberculosis of the hip. The presentation is not exhaustive but offers a working plan that is feasible and logical.

In the section on treatment great stress is laid on the importance of determining the type of joint that one aims to get—a movable or an immovable joint—and the therapeutic measures suggested vary with the ultimate result in view.

A short note on the mechanics of the hip-joint, with particular reference to the effect of osteotomy, adds to the value of the book.

I. W. N.

The Aspergilli. By CHARLES THOM AND MARGARET CHURCH. 272 pp. $5.00. (*The Williams & Wilkins Co., Baltimore, 1926.*)

Aspergillus represents one of the most common groups of molds in nature. Some of the organisms belonging to this group have found extensive industrial application, as in the preparation of various proteolytic and diastatic enzymes, gallic acid fermentation, manufacture of citric acid, saccharification of mashes for alcoholic fermentation and soy sauce manufacture, production of syrup, invert sugar, coffee fermentation, fish fermentation, etc. Some of the species cause an important disease in birds; some bring about molding of nuts, tobacco and leather; some are parasitic on onions. A number of species are found in the soil and in foodstuffs, while many forms have been used for various biochemical investigations.

The authors have succeeded in bringing together and digesting, in a clear and systematic manner, a vast amount of information dealing with the morphological and biological characteristics, as well as with the taxonomy of this group of organisms and the utilization of the activities of various species for industrial purposes. The major part of the book is devoted to the nomenclature and classification of the Aspergilli, and comprises a discussion of over 300 different species, largely a result of the investigations of the authors themselves. An extensive literature and an index are appended.

The book is well printed. The authors should be commended for condensing the extensive literature on this subject into 272 pages, and the publishers for bringing out this valuable monograph.

S. A. W.

Intestinal Tuberculosis. Its Importance, Diagnosis and Treatment. A Study of the Secondary Ulcerative Type. By LAWRASON BROWN, M.D., Chairman of the Medical Board of The Trudeau Sanatorium and HOMER L. SAMPSON, Roentgenographer of the Trudeau Sanatorium, Saranac Lake, N. Y. 304 pp. (*Lea and Febiger, New York, 1926.*)

This monograph constitutes an excellent treatise on intestinal tuberculosis. The subject is covered in a thorough and satisfactory way. Brief chapters on the anatomy and physiology of the intestinal tract are followed by a longer discussion of the pathological anatomy and the clinical symptoms of the disorder. Diagnosis is fully considered and special attention is given to the importance of roentgenological study. This method of diagnosis had been previously elaborated by the author and its value established by careful clinical and pathological investigation. Indeed, to point out the great helpfulness of roentgenological examinations would seem to be the chief purpose of the book. An exhaustive bibliography is appended.

This is the first of a series of monographs on tuberculosis to be published by the Trudeau Foundation. It sets a high standard of excellence, and if the promised volumes equal it in interest and thoroughness, they will be most welcome, for publications that deal exhaustively and authoritatively with a special phase of medicine are the ones that are most useful and satisfying. Intestinal tuberculosis is a small department of tuberculous disease, but anyone interested in the condition or desirous to be informed about it will here find all of the pertinent facts satisfactorily assembled and discussed.

L. H.

BOOKS RECEIVED

A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. By PERCIVAL BAILEY AND HARVEY CUSHING. With 108 illustrations. 1926. 8°. 175 pages. J. B. Lippincott Company, Philadelphia.

Collected Papers by the Staff of the Henry Ford Hospital. [First series 1915–1925.] With 151 illustrations and 42 charts. 1926. 8°. 634 pages. Paul B. Hoeber, Inc., New York City. $8.00.

Annals of the "Pickett-Thomson" Research Laboratory. Vol. 1, No. 1, July, 1924. London.

Advising the Tuberculous about Employment. By W. I. HAMILTON AND T. B. KIDNER. 1926. 12°. 171 pages. The Williams & Wilkins Company. Baltimore. $2.00.

The Bacteriophage and its Behavior. By F. D'HERELLE, M.D. Translated by George H. Smith, Ph.D. 1926. 8°. 629 pages. The Williams & Wilkins Company, Baltimore. $8.00.

An Introduction to the Study of X-Rays and Radium. By HECTOR A. COLWELL, M.B. (Lond.), D.P.H. (Oxf.) and CECIL P. G. WAKELEY, F.R.C.S. (Eng.), F.R.S. (Edin.) 1926, 8°. 203 pages. Oxford Medical Publications. Oxford University Press, London. $3.35.

Neuritis and Neuralgia. By WILFRED HARRIS. 1926. 8°. 418 pages. Oxford Medical Publications. Oxford University Press, London. $4.00.

The Diagnosis, Treatment and End Results of Tuberculous Disease of the Hip Joint. By GEORGE PERKINS, M.Ch. Oxon., F.R.C.S. Eng. 1926. 8°. 118 pages. Oxford Medical Publications. Oxford University Press, London. $1.75.

The Charaka Club Proceedings. Vol. VI, 1925. 8°. 145 pages. Paul B. Hoeber, New York. $4.00.

Malignant Disease of the Testicle. Its Pathology, Diagnosis, and Treatment. By HAROLD R. DEW, M.B., B.S. (Melbourne), F.R.S.C. With 52 illustrations including 5 coloured plates. 1926. 8°. 168 pages. Paul B. Hoeber, New York. $7.00.

The Private Practitioner as Pioneer in Preventive Medicine. Being the Annual Oration of the Hunterian Society: 1926. By SIR GEORGE NEWMAN, K.C.B., M.D., D.C.L. 1926. 8°. 47 pages. Oxford University Press, London. $0.30.

American Surgical Association Transactions. Edited by John H. Jopson, M.D. Volume the forty-third. 1925. 8°. 986 pages. Philadelphia.

Vital Capacity of the Lungs. A Handbook for Clinicians and Others Interested in the Examination of the Heart and Lungs both in Health and Disease. By J. A. MYERS, M.S., Ph.D., M.D. With introduction by S. Marx White, B.S., M.D., F.A.C.P. 1925. 8°. 140 pages. The Williams & Wilkins Company, Baltimore. $3.25.

A Handbook for Senior Nurses and Midwives. By J. K. WATSON, M.D. (Edin.), Capt., R.A.M.C. 1926. 8°. 554 pages. Oxford Medical Publications. Humphrey Milford, London. $4.00.

Diseases of Infants and Children. By HENRY DWIGHT CHAPIN, A.M., M.D. and LAWRENCE THOMAS ROYSTER, M.D. Fifth revised edition. 1925. 8°. 633 pages. William Wood and Company, New York. $6.00.

Nephritis. By HERMAN ELWYN, M.D. 1926. 8°. 347 pages. The Macmillan Company, New York. $5.00.

Food for the Diabetic. What to eat and how to calculate it with common household measures. By MARY PASCOE HUDDLESON. With an introduction by Nellis Barnes Foster, M.D. Second edition revised. 1926. 8°. 83 pages. The Macmillan Company, New York. $1.25.

Operative Cystoscopy. By E. CANNY RYALL, F.R.C.S. With 115 plates containing 670 original illustrations of which 528 are coloured. 1925. Fol. C. V. Mosby Co., St. Louis. $25.00.

Cancer of the Rectum. Being the Lettsomian Lectures delivered before the Medical Society of London, on February 19th, March 7th, and March 26th, 1923. By ERNEST MILES, F.R.C.S. 1926. 8°. 72 pages. 7/6. Harrison and Sons, Ltd., London.

Chemistry and Recent Progress in Medicine. By JULIUS STIEGLITZ. The Johns Hopkins University, School of Medicine, the Charles E. Dohme Memorial Lectureship, Second Course, 1924. 1926. 8°. 62 pages. The Williams & Wilkins Company, Baltimore. $1.50.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by HENRY W. CATTELL, A.M., M.D., with the collaboration of Chas. H. Mayo, M.D. [*et al.*] Thirty-sixth series, vol. 1, 1926. 8°. J. B. Lippincott Company, Philadelphia and London. $2.50.

American Gynecological Society. Transactions. Volume 50 for the year 1925. Edited by Arthur H. Curtis, M.D. 8°. 317 pages. William J. Dorman, Philadelphia.

Facts on the Heart. By RICHARD C. CABOT, M.D. Illustrated. 1926. 8°. 781 pages. Illustrated. W. B. Saunders Company, Philadelphia and London. $7.50.

Archives of the Andrew Todd McClintock Memorial Foundation for the Study of Diseases of the Alimentary Canal. Volume 1. Pleomorphism in Bacterial Protoplasm. A Study in Psittacosis. By ANDREW TODD MCCLINTOCK, M.D. Privately Printed. 1925. 8°. 240 pages.

New Jersey Department of Health. Forty-Eighth Annual Report of the Department of Health of the State of New Jersey, 1925. 8°. 280 pages.

Psychotherapy. Mental Elements in the Treatment of Disease. By EDWARD WYLLYS TAYLOR. Harvard Health Talks. 1926. 12°. 53 pages. Harvard University Press, Cambridge. $1.00.

Comparative Physiology. By LANCELOT T. HOGBEN, M.A. (Cantab.), D.Sc. (Lond.) 1926. 8°. 219 pages. The Macmillan Company, New York. $7.50.

Gastric Function in Health and Disease. By JOHN A. RYLE, M.D. (Lond.), F.R.C.P. 1926. 8°. 152 pages. $2.75. Oxford Medical Publications. Oxford University Press, London.

Montefiore Hospital for Chronic Diseases. Collected Reprints. Volume iv, 1925. New York City.

Young's Practice of Urology. Based on a study of 12,500 cases. By HUGH H. YOUNG and DAVID M. DAVIS. With the collaboration of Franklin P. Johnson. With over 1000 illustrations, 20 being color plates by William P. Didusch. Volume I, 746 pages; Volume II, 738 pages. 1926. 4°. W. B. Saunders Company, Philadelphia and London. $25.00.

Modern Methods of Amputation. By THOMAS G. ORR, A.B., M.D., F.A.C.S. One hundred twenty-five illustrations. 1926. 8°. 117 pages. The C.V. Mosby Company, St. Louis. $3.50.

Handbook of Diseases of the Rectum. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S. With two hundred fifty-two illustrations, mostly original, and five colored plates. Fourth edition revised and rewritten. 1926. 8°. 403 pages. The C. V. Mosby Company, St. Louis. $6.50.

Physics and Chemistry for Nurses. By A. R. BLISS, JR., A.M., Phm.D., M.D., F.A.I.C. and A. H. OLIVE, A.M., Ph.Ch., Phm.D. 70 illustrations. Fourth edition thoroughly revised and rewritten and conforming to the requirements of the standard curriculum (1924) of the National League of Nursing Education. 1926. 8°. 190 pages. J. B. Lippincott Company, Philadelphia. $2.50.